The cognition of non-verbal sound in dementia

A Thesis
presented for the degree of
Doctor of Philosophy

by

Johanna Christine Goll

The Dementia Research Centre,
Institute of Neurology,
University College London (UCL)

2011

Declaration

I, Johanna C Goll confirm that the work presented in this thesis is my own. Where information has been derived from other sources, or conducted in collaboration with other researchers, I confirm that this has been indicated (see section 8.4). All participating subjects gave informed consent and all experimental work was carried out with the approval of University College London Hospitals (UCLH) Research Ethics Committee, according to guidelines established by the Declaration of Helsinki.

Johanna C Goll Date

Acknowledgements

Many people contributed to the work described in this thesis. I would like to extend particular thanks to all of the patients, carers, and control subjects who participated in this research, many of whom travelled far to devote several days to the completion of neuropsychological tests and brain scans; their remarkable enthusiasm, generosity, and courage made data collection a truly enjoyable and enriching experience. I will remain indebted to **Jason Warren**, my primary supervisor, who came up with the excellent idea to pursue auditory neuropsychological research in dementia, and who also obtained the necessary funding to support me during my studies. More importantly however, Jason provided a constant and vital source of invaluable scientific knowledge, which he gave freely, enthusiastically, and tirelessly; I am extremely grateful to have had the opportunity to learn from such an exceptional scientist. **Sebastian Crutch**, my secondary supervisor, offered astute and judicious scientific advice throughout, and was never too busy to help; in particular, I would not have been able to develop the behavioural tests that form the cornerstones of this work without Seb's superb neuropsychological guidance. I am also hugely grateful to **Gerard Ridgway** who patiently tutored me in the use of SPM; additionally, Ged was always happy to offer advice on a wide range of neuroimaging issues, enabling the development of far more sophisticated fMRI analysis methods than would otherwise have been possible. Similarly, I am grateful to **Susie Baker** who kindly gave up her time to teach me all I needed to know about VBM, and more. I have completed this work alongside several other research assistants at the Dementia Research Centre (DRC), and am sincerely grateful to them all for the countless occasions when they helped me, whether in the practical matters of patient testing, or through the provision of much appreciated moral support: **Julia Hailstone**, **Aisling Buckley**, **Manja Lehmann**, **Mary Keilty**, **Sarah Connell**, **Katy Randelsome**. For support during the analysis of often very complex datasets, I am extremely thankful to the DRC statistics team: **Chris Frost**, **Lois Kim** and **Jonathon Bartlett**. **Elizabeth Warrington** generously shared her considerable neuropsychological expertise on numerous occasions. Staff at the Functional Imaging Laboratory provided essential neuroimaging support: I am grateful to **Nikolaus Weiskopf** for help in optimising MRI acquisition parameters, and to **Janice Glensman**, **Sheila Lee**, and **Kristian Johannesson** for assistance in acquiring scans. **Frederic Theunissen**, **Timothy Griffiths**, **Manon Grube** and **Roy Patterson** generously shared their methods for digital sound synthesis and manipulation, enabling me to use a sophisticated range of stimuli in my behavioural tests. I would also like to thank several of the clinical research fellows at the DRC who frequently put me in contact with patients who were suitable for research: **Rohani Omar**, **Jonathon Rohrer**, **Colin Mahoney**, **Natalie Ryan**. I am also immensely grateful to the many other DRC staff members who make the department an exceptionally positive and friendly environment to work within. Finally, I could not have completed this work without the support and companionship of my family and friends; I'd particularly like to thank **my parents**, **brothers and grandma** for their absolute faith in my abilities, **Lia** for teaching me to how to stay bendy and relaxed, and **Tom** for his love, and the big red emergency teleportation button!

Summary

A growing body of functional imaging studies provides considerable insight into cortical networks for non-verbal auditory processing. However, determination of the essential cognitive and anatomical components of these networks depends upon the study of damaged brains, and yet, auditory neuropsychology is little studied and poorly understood. Whilst naturally occurring lesions that selectively disrupt auditory processes are rare, increasing evidence suggests that degenerative diseases target functional networks implicated in non-verbal auditory processing. Furthermore, a small but significant auditory neuropsychological literature shows that dementia can lead to impairments of non-verbal sound processing. This thesis comprises a series of studies designed to reveal deficits of non-verbal auditory processing in four distinct dementia syndromes: three variants of primary progressive aphasia (semantic dementia, SD; progressive non-fluent aphasia, PNFA; logopenic aphasia, LPA), and typical Alzheimer's disease (AD). The first two studies (Chapters 2 and 3) involve the development of two novel non-verbal auditory neuropsychological batteries, including tests to examine perceptual property, apperceptive, and semantic stages of processing; the subsequent use of these batteries reveals syndrome-specific profiles of non-verbal auditory impairment. Next, a detailed psychoacoustic assessment of two single cases (Chapter 4) provides evidence for specific disorders of auditory property and object processing. A further study (Chapter 5) comprises the examination of non-verbal auditory object processing in SD using functional magnetic resonance imaging (fMRI); results suggest that auditory object recognition depends upon a distributed temporo-parietal network involving closely associated mechanisms of perceptual and semantic processing. Finally, novel neuropsychological assessments are used to reveal the selective impairment of auditory scene analysis in AD (Chapter 6). Together, these neuropsychological findings provide novel insights into the organisation of cortical networks for non-verbal auditory cognition.

Contents

Figures

Tables

Sounds

Auditory stimuli used in current work are presented on a CD (in .wav form), which can be found in the back cover of this thesis. All sounds included on the CD are listed below, and more details can be found in the relevant sections of text.

Chapter	Sound number	Sound description	Thesis section
1	1	Pure tone (200Hz)	1.3.1
	2	Pure tone (400Hz)	
	3	Hammer 1	1.3.2
	4	Hammer 2	
	5	Baby gurgle	
	6	Chainsaw	
	7	Sheep baa	
	8	Phone 1	
	9	Phone 2	
	10	January	
	11	December	
2	12	Property	2.6.3.2
	13	Apperceptive (raw)	2.6.3.3
	14	Apperceptive (spectrally inverted)	
	15	Semantic	2.6.3.4
3	16	Pitch change detection (same)	3.4.3.1.1
	17	Pitch change detection (up)	
	18	Pitch change direction (down)	
	19	Pitch change direction (up)	
	20	Timbre (down)	3.4.3.1.2
	21	Timbre (up)	
	22	Dog (big)	3.4.3.1.3
	23	Dog (small)	
	24	Unfamiliar animal (big)	
	25	Unfamiliar animal (small)	
	26	Apperceptive (tool)	3.4.3.1.4
	27	Apperceptive (animal)	
	28	Semantic (inside)	3.4.3.1.5
	29	Semantic (outside)	
4	30	Pitch detection (same)	4.5.1.1
	31	Pitch detection (up)	
	32	Pitch direction (down)	
	33	Pitch direction (up)	
	34	Timbre (up)	4.5.1.2
	35	Timbre (down)	
	36	Isochrony: property processing baseline (isochronous)	4.5.1.3
	37	Isochrony: property processing baseline (anisochronous)	
	38	Degraded (animal 1)	4.5.1.4
	39	Degraded (animal 2)	
	40	Degraded (tool 1)	
	41	Degraded (tool 2)	

Chapter	Sound number	Sound description	Thesis section
4	42	Isochrony: scale processing baseline (same)	4.5.1.6
	43	Isochrony: scale processing baseline (different)	
	44	Scale (same)	
	45	Scale (different)	
	46	Pitch - continuous (up)	4.6.1
	47	Pitch - continuous (down)	
	48	Pitch - segmented (up)	
	49	Pitch - segmented (down)	
	50	Intensity - continuous (up)	
	51	Intensity - continuous (down)	
	52	Intensity - segmented (up)	
	53	Intensity - segmented (down)	
	54	Click fusion (no gap)	4.7.1.1
	55	Click fusion (level 1)	
	56	Click fusion (level 9)	
	57	Click fusion (level 18)	
	58	Spectral (same)	4.7.1.2
	59	Spectral (different - level 1)	
	60	Spectral (different - level 5)	
	61	Spectral (different - level 10)	
	62	Spectral (different - level 15)	
	63	Spectral (different - level 19)	
	64	Temporal (same)	
	65	Temporal (different - level 1)	
	66	Temporal (different - level 5)	
	67	Temporal (different - level 10)	
	68	Temporal (different - level 15)	
	69	Temporal (different - level 19)	
5	70	Animal 1 (meaningful)	5.4.2
	71	Animal 1 (meaningless)	
	72	Animal 2 (meaningful)	
	73	Animal 2 (meaningless)	
	74	Tool 1 (meaningful)	
	75	Tool 1 (meaningless)	
	76	Tool 2 (meaningful)	
	77	Tool 2 (meaningless)	
6	78	Segregation - baseline perceptual cue (changing)	6.5.4.2
	79	Segregation - baseline perceptual cue (constant)	
	80	Segregation - baseline task requirement (intermittent)	6.5.4.3
	81	Segregation - baseline task requirement (continuous)	
	82	Segregation - main task (intermittent)	6.5.4.1
	83	Segregation - main task (continuous)	
	84	Grouping - baseline perceptual cue (changing)	6.5.5.2
	85	Grouping - baseline perceptual cue (constant)	
	86	Grouping - baseline task requirement (even)	6.5.5.3
	87	Grouping - baseline task requirement (uneven)	
	88	Grouping - main task (even)	6.5.5.1
	89	Grouping - main task (uneven)	

1 Introduction

Few studies have investigated the neuropsychology of non-verbal auditory processing, and as a result, relevant cognitive mechanisms remain poorly understood. In contrast, the neuropsychology of visual object processing has been frequently investigated; in this literature, a taxonomy of patient deficits is well established, including various perceptual and semantic syndromes. Although preliminary evidence suggests the existence of broadly analogous auditory deficits, and thus similar cognitive processing stages (Griffiths et al., 1999; Simons and Lambon Ralph, 1999), the extent to which auditory neuropsychology can be mapped onto the framework offered by visual neuropsychology is currently unknown. Importantly, the underdeveloped taxonomy of non-verbal auditory neuropsychology limits inferences that can be drawn about auditory cognition more generally. Specifically, whilst a growing body of functional imaging studies associates specific stages of non-verbal auditory cognition with particular anatomical substrates, the study of damaged brains is required to determine which components are essential rather than subsidiary (Price and Friston, 2002). Work presented in this thesis therefore seeks to refine the taxonomy of non-verbal auditory neuropsychology through the assessment of neurological patient populations, in order to develop understanding of the auditory brain.

Increasingly, evidence suggests that the healthy human brain consists of multiple large-scale distributed neural networks comprising clusters of neurons that are co-activated during particular cognitive functions (Meslaum, 2009). Of relevance here, such distributed neural networks are increasingly implicated in non-verbal auditory cognition by functional imaging studies of healthy human subjects (Wessinger et al., 2001; Griffiths and Warren, 2002; Griffiths and Warren, 2004; Griffiths et al., 2007; Peretz et al., 2009; Staeren et al., 2009; Hyde et al., 2010; Leaver and Rauschecker, 2010), and anatomical studies of primates (Rauschecker and Tian, 2000; Kaas, and Hackett, 2000; see Romanski and Averbeck, 2009). At the same time, the degenerative dementias are a group of neurological diseases characterized by the selective anatomical degeneration of functionally coherent neural networks (Sonty et al., 2007; Seeley et al., 2009; Mesulam, 2009; Buckner et al., 2009; Zhou et al., 2010).

Therefore, the non-verbal auditory neuropsychological assessment of dementia patients may illuminate the impact of functional network degeneration upon sound processing, thus providing insight into corresponding mechanisms in the healthy brain. Notably, such information is not necessarily provided by the study of other neurological populations, including stroke patients, in which the profile of brain damage is driven by structural factors (blood vessel organisation) rather than functional connectivity. Thus, the investigations of this thesis will seek to examine non-verbal auditory processing in a range of dementia syndromes.

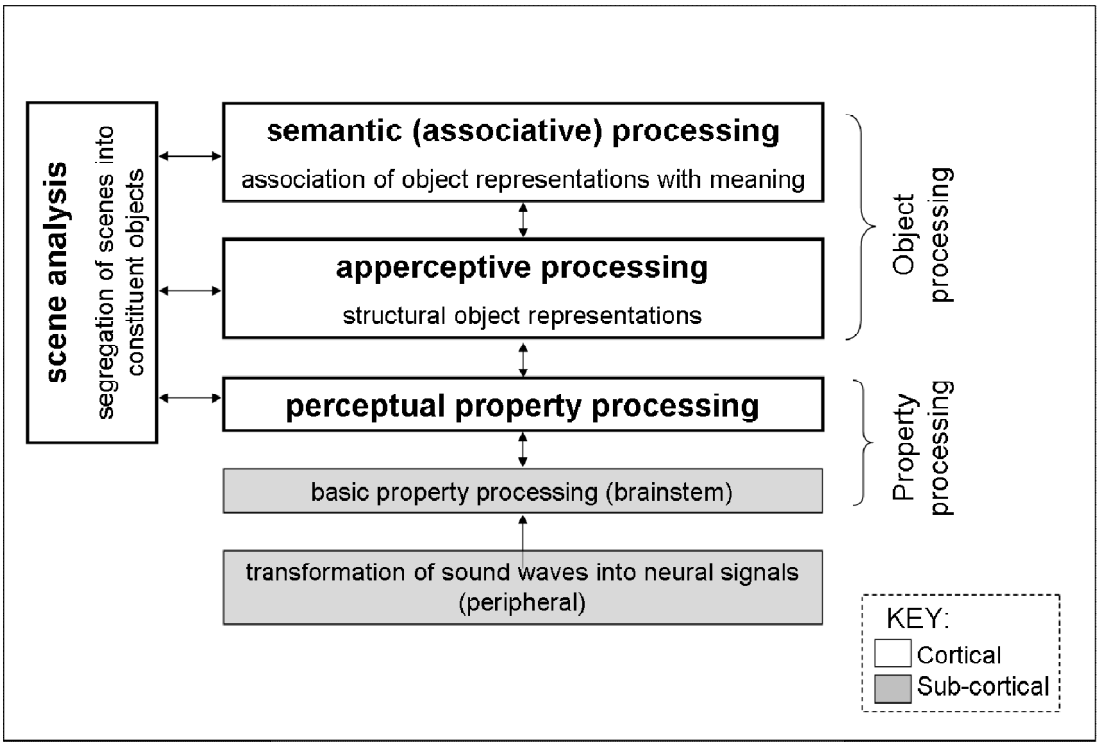
In particular, this thesis will examine two subgroups of the degenerative dementias: syndromes of primary progressive aphasia (PPA) typically caused by frontotemporal lobar degeneration (FTLD) including semantic dementia (SD), progressive non-fluent aphasia (PNFA), and logopenic (phonological) aphasia (LPA); and the syndrome of typical Alzheimer's disease (AD). Previous neuropsychological research involving these syndromes has tended to focus upon their most prominent and incapacitating symptoms, namely deficits of speech and language in PPA, and episodic memory in AD. However, whilst empirical data are currently lacking, evidence suggests that all four syndrome groups are likely to involve accompanying auditory processing disorders. For example, emerging neuropsychological studies in both PPA and AD provide evidence for a variety of non-verbal auditory processing impairments. Additionally, each syndrome leads to the cortical degeneration of functionally coherent brain networks that coincide with substrates implicated in non-verbal auditory cognitive processing in the healthy brain (Seeley et al., 2009). Furthermore, since these different syndromes involve overlapping but distinct profiles of cortical damage, networks of auditory processing are likely to be disrupted in a syndrome-specific manner. Finally, the relatively focal nature of brain damage in dementia, and particularly in PPA, suggests that patients may additionally show selective impairments affecting restricted sub-processes of auditory cognition. Thus, the investigations of this thesis will seek to compare patterns of non-verbal auditory deficits and anatomical damage between the syndromes of SD, PNFA, LPA and AD, in order to further understanding of the auditory brain.

Before embarking upon a description of the relevant literature, it is necessary to outline a number of key concepts relevant to the study of auditory processing in dementia. Therefore, Chapter 1 begins with sections to describe the broad stages of non-verbal auditory processing (section 1.1), the concept of an auditory object (section 1.2), and the physical structure of sounds (section 1.3). After outlining the main foci of current investigations (section 1.4), a review of the literature of non-verbal cortical auditory processing deficits is then presented (section 1.5). Next, the patient groups to be investigated are described in detail (section 1.6). In the final section of Chapter 1, key empirical hypotheses adopted by the present investigations are given (section 1.7). Throughout this chapter and the remainder of this thesis, auditory examples that can be listened to using the CD provided (inside the back cover) are referenced. Finally, a glossary of technical terms that may be useful whilst reading this chapter, alongside a list of commonly used abbreviations, is provided in an appendix (section 8.1).

1.1 Stages of non-verbal auditory processing

Non-verbal auditory cognition is likely to comprise multiple functions involving both the analysis of auditory input and the production of auditory output. However, output functions (e.g., the production of non-verbal vocalisations or prosody) will not be explicitly studied within this thesis, and the term non-verbal auditory processing will be reserved for 'input' processes involving the perception and recognition of non-verbal auditory information. Although auditory neuropsychology remains poorly understood, available evidence suggests that non-verbal auditory processing deficits may broadly align with those described in the visual modality (Griffiths et al., 1999; Simons and Lambon Ralph, 1999). Thus, based upon the findings of visual neuropsychology (e.g., De Renzi et al., 1969; Warrington and Taylor, 1978), an initial and simplified overview of the main processing stages of non-verbal auditory processing is proposed in Figure 1.1; current work will seek to establish the validity of this cross-modal comparison. In particular, this thesis will focus upon the subset of these cognitive stages that are associated with processing in the cerebral cortex; however, mechanisms associated with the peripheral sensory systems of the ear and the sub-cortical auditory pathways will first be described, to enable their differentiation from cortical processes.

Figure 1.1 A preliminary model of non-verbal auditory processing



1.1.1 Peripheral auditory processing: transformation of sound waves into neural signals

The peripheral auditory processing system, including the eardrum and the cochlea, enables the transformation of sound waves into neural signals for subsequent cerebral processing. Sound waves are initially detected as mechanical vibrations on the eardrum (the tympanic membrane). The cochlea is a spiral-shaped entity containing almost incompressible fluid, which, if unwound, can be divided lengthwise by the basilar membrane (BM). Vibrations are passed to the BM, which as a result of its physical structure, responds differently to different sounds; specifically, the location of maximal vibration along the length of the BM varies with sound frequency. This spatiotopic encoding of sound frequency is fed forwards by hair cells, which transduce the mechanical vibrations of the BM into neural signals and pass them onto the nerve fibres of the auditory nerve (AN).

1.1.2 Dysfunctions of peripheral auditory processing: peripheral hearing loss

Peripheral hearing loss occurs following damage to the peripheral auditory system, and causes a complete or partial inability to detect and/or perceive all sounds. Patients with peripheral hearing loss exhibit increased sound detection thresholds and various deficits of complex sound perception including reduced spectral and temporal resolution (Griffiths et al., 1999). Various clinical tests are commonly used to detect and discriminate between the different forms of peripheral hearing loss (e.g., pure tone audiometry, otoacoustic emissions, electrocochleography). Presbycusis is an age-related form of peripheral hearing loss, involving a progressive reduction in the ability to hear high frequencies. Although presbycusis is typically partial and relatively mild, the syndrome is common in older adult populations (Liu and Yan, 2007), and therefore by extension, dementia populations. Thus, the investigations contained in this thesis will measure peripheral hearing loss and account for its effect upon neuropsychological assessments of auditory cognition.

1.1.3 Sub-cortical auditory processing

The sub-cortical auditory system, consisting of the ascending auditory pathways that link the auditory nerve with the cerebral cortex, perform the first and most basic analyses of sound signals. The pathways flow through the brainstem, via several nuclear complexes which function as neural signal relay stations: the cochlear nuclear complex (CNC), the superior olivary nucleus, the inferior colliculus (IC), and the medial geniculate body. Along the way, the pathways diverge into multiple parallel tracts on both sides of the brainstem. Within these multiple pathways, a number of different auditory properties are represented and subsequently integrated with one another, such that representations increase in complexity as the pathway ascends (e.g., Young, 2010). For example, single cells at lower levels (AN, CNC) may contain representations of a particular frequency at one ear, whilst single cells at higher levels (IC) may represent a range of frequencies across both ears.

Representations of sounds in the sub-cortical pathways tend to take the form of more or less direct mappings of the physical structure of sound, i.e. they tend to be isomorphic. However, sound representations required for non-verbal auditory processing tasks such as sound recognition are likely to exhibit more complexity. For example, the auditory system is required to generate a consistent representation of a particular environmental sound in physically different contexts, e.g., when presented with varying acoustic properties or against varying background scenes. The direct isomorphic representations associated with sub-cortical regions are therefore unlikely in themselves to facilitate all aspects of non-verbal auditory processing, although their information content feeds forwards to support more complex processes.

1.1.4 Cortical auditory processing

The outputs of sub-cortical auditory processes are passed onto dedicated auditory processing regions in the cerebral cortex, including various areas of the temporal and inferior parietal lobes. Here, evidence suggests that sound representations have greater complexity than those found sub-cortically, and may therefore facilitate non-verbal auditory processes such as object recognition. For example, cortical sound representations tend to be perceptual

rather than isomorphic, i.e., they contain complex non-linear mappings between sound structure and sound identity. This composition would enable the emphasis of properties that are particularly relevant to certain sounds (e.g., the characteristic frequencies of a friend's voice) and the de-emphasis of unimportant properties (e.g., those of background noise). Such cortical perceptual representations would therefore provide the basis for non-verbal auditory processing tasks including the identification of particular environmental sounds in physically different contexts. Thus, the current investigation will focus upon cortical rather than sub-cortical sound processing.

1.1.4.1 Cortical auditory processing in animal models

Knowledge about the anatomy of human auditory cortical processing is informed by a large literature in the macaque (e.g., Kaas and Hackett, 2000). This work shows that dedicated auditory cortical areas are located within the superior temporal plane (STP) and the anterior two thirds of the superior temporal gyrus (STG). Information is first processed within a central 'core' region, the first cortical connection of the ascending auditory pathways, which is located medially, midway along the STP. Next, information is passed to a number of anatomically discrete 'belt' and 'parabelt' regions which surround the core. Finally, information is fed forward to a range of closely connected areas extrinsic to the dedicated auditory processing region, including the posterior STG, the inferior parietal lobe and the lateral prefrontal cortices. Core, belt, parabelt and extrinsic regions in the macaque are conceptualised as consecutive levels in a processing hierarchy; as information progresses through this hierarchy, evidence suggests that auditory representations become increasingly complex, and increasingly integrated with non-auditory information to form cross-modal representations (Kaas and Hackett, 2000; Poremba et al., 2003).

1.1.4.2 Cortical auditory processing in humans

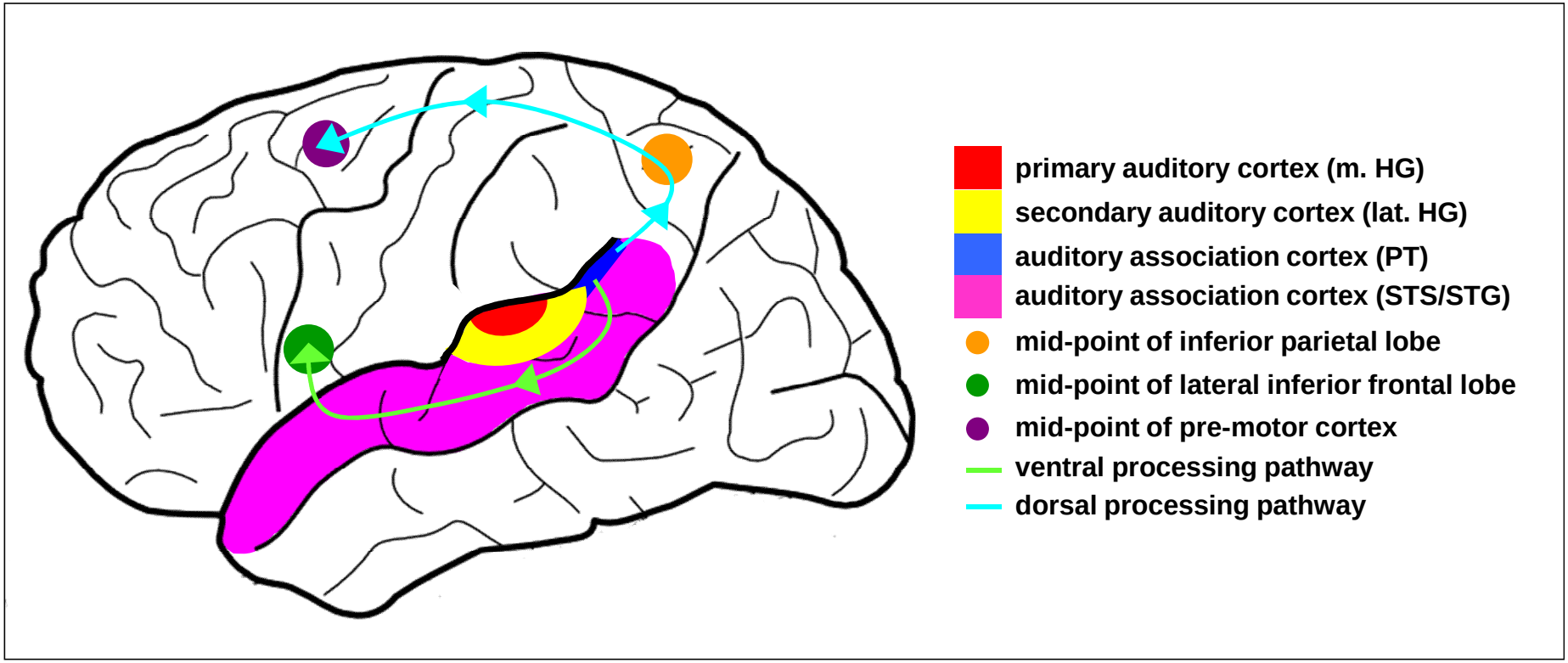
Substantial evidence suggests that the human auditory brain exhibits a similar structural organisation to that of the macaque, consisting of hierarchically organised processing regions in which auditory representations become

increasingly complex, and increasingly integrated with information from other modalities and brain processes (Binder et al., 2000; Wessinger et al., 2001; Leaver and Rauschecker, 2010). However, sub-regions of the human cortex have been mapped out in much less detail, partly because suitable non-invasive techniques suffer from reduced spatial resolution, and partly due to a high level of inter-individual variation in the macroscopic structural organisation of human auditory areas. Additionally, it has been challenging to define the role of any sub-region precisely, and uncertainties are likely to become amplified when considering more complex processes. Therefore, when considering the anatomical organisation of auditory processing, this thesis will focus upon distinctions between four broad sub-regions (see Figure 1.2): primary auditory cortex, secondary auditory cortex, planum temporale, and auditory association cortex.

Human cortical auditory processing (Figure 1.2) begins in the primary auditory cortex (PAC), which is the first cortical connection of the ascending auditory pathways. The PAC is physically located midway along the STP in medial Heschl's gyrus (HG), and is buried in the convexity of the Sylvian fissure such that it can only be viewed by removing the overlying cortex. This region is broadly analogous to the core region in the macaque, and preferentially encodes a range of basic auditory perceptual properties such as frequency. In particular, functional imaging work has shown that human PAC has a tonotopic organisation, i.e., a systematic spatial arrangement of the sound frequencies to which neurons are most responsive (e.g., Humphries et al., 2010). From the PAC, information is passed to nearby regions, in which auditory properties of increasing complexity are represented. For example, the secondary auditory cortex, situated in lateral HG, encodes pitch information (Patterson et al., 2002; Penagos et al., 2004; Gutschalk et al., 2004; Schneider et al., 2005). Additionally, a wide range of further auditory properties (e.g., spectral, temporal, spectrotemporal shapes, see section 1.3) are represented within particular portions of posterior-dorsal auditory association cortices (Giraud et al., 2000; Zatorre and Belin, 2001; Poeppel, 2003; Schönwiesner et al., 2005; Boemio et al., 2005; Altmann et al., 2010). Next, information is fed into a sub-region of auditory association cortex known as the planum temporale (PT) which lies just posterior to HG; here, evidence suggests that the many different types of

auditory properties are combined into preliminary representations of whole auditory objects (Griffiths and Warren, 2002; Warren et al., 2005b). Subsequently, these preliminary object representations are elaborated within distinct ventral and dorsal auditory processing pathways, which have been proposed on electrophysiological grounds (Kaas and Hackett, 2000). As information flows through the ventral pathway in an anterior-ventral direction along the superior temporal gyrus and sulcus (STS/G), representations contain progressively more detailed (perceptual and semantic) object information (Leaver and Rauschecker, 2010). In particular, human imaging studies suggest that the anterior-ventral auditory association cortices includes circumscribed sub-regions which represent particular auditory object categories, such as voices, speech, animal vocalisations and musical instruments (Belin et al., 2002; Lewis et al., 2005; Lewis et al., 2006; Leaver and Rauschecker, 2010). In contrast, the dorsal pathway, which flows in a posterior-dorsal direction from the PT via the posterior temporal and inferior parietal lobes to the pre-motor cortex, is held to facilitate the representation of auditory space (Warren et al., 2002; Warren and Griffiths, 2003), and the integration of human action and speech sounds with relevant motor information (e.g., Lewis et al., 2005; Lewis et al., 2006; Lewis et al., 2010). Finally, information processing within both pathways is modulated by the action of extrinsic regions such as the lateral inferior frontal lobe (IFL), which may help to allocate attentional resources to behaviourally important sounds (e.g., Schönwiesner et al., 2007). Taken together, human evidence strongly suggests a hierarchical organisation of sound processing in which auditory representations become increasingly complex, and increasingly integrated with other cognitive processes, as information flows through both the ventral and dorsal auditory processing pathways.

Figure 1.2 Schematic of the main cortical regions and pathways associated with auditory processing in the human brain



For visualisation purposes, the primary auditory cortex and planum temporale are shown on the surface of the superior temporal gyrus; however, in a real brain they are buried within the convexity of the Sylvian fissure in the medial portion of the superior temporal plane such that they can only be viewed by removing the overlying cortex. KEY: m., medial; HG, Heschl's gyrus; lat., lateral; PT, planum temporale; STS/STG, superior temporal sulcus/gyrus.

1.2 The definition of auditory objects

As indicated, this thesis will be concerned with the neuropsychology of non-verbal auditory cognition, and the majority of investigations will focus upon the processing of auditory objects. However, the definition, as well as the psychological validity, of auditory objects is currently a topic of controversy (e.g. Kubovy and Van Valkenburg, 2001; Griffiths and Warren, 2004). It is therefore necessary to discuss these issues and develop a definition of auditory objects that has both practical and theoretical utility for proposed investigations.

1.2.1 The definition of visual objects

For the neuropsychologist, the concept of an 'object' is likely to suggest the familiar objects of vision: accordingly, in defining auditory objects one can turn first to definitions of visual objects. Generally, visual objects are held to be collections of visual sensory data that are bound in a single perceptual representation to reflect a single entity in the physical world, and are thereby disambiguated from other nearby objects and the visual scene. Beginning with the classical studies of the Gestalt school, the organising principles followed by the sensory system when combining sensory data into visual objects have been specified in some detail (see e.g., Ellis, 1938). Such principles generally operate to increase perceptual coherency within (versus between) objects, according to context. Thus, the principle of 'similarity' (for example) leads to the grouping of sensory elements that share characteristics, such as colour or texture (Bregman, 1990, pp19). Additionally, within many visual scenes there are multiple, hierarchically organised levels of visual objects (e.g., Feldman, 2003); for example, a particular scene may contain a tree-object, which may contain a branch-object, which may contain a leaf-object. As a result, different visual objects can often be found simultaneously within the same sensory data, and their prominence may vary with the perceiver and the context (e.g., branches are useful if one wants to climb a tree, but leaves may be more useful if one wants to identify the species). Thus, for present purposes, two key principles are emphasised: (i) that visual objects are collections of visual sensory data bound in a single perceptual representation and disambiguated from the visual scene, and (ii) that within the same visual sensory data, different visual objects

are present simultaneously, and may vary in prominence according to a perceiver's behavioural goals.

1.2.2 Towards a definition of auditory objects

There are a number of similarities between object processing in the visual and auditory modalities. Firstly, evidence suggests that the formation of auditory objects is guided by processes analogous to the Gestalt principles described in the visual modality, which increase perceptual coherency within (versus between) objects. For example, in the formation of auditory objects the aforementioned Gestalt principle of 'similarity' leads to the grouping of sensory elements that share particular auditory properties, such as pitch or timbre (Bregman, 1990, pp19). Secondly, in both the visual and auditory modalities, the same sensory data often contain many different objects simultaneously. In the auditory modality this is clearest for complex auditory environments containing multiple sound sources, but may apply even to objects generated by single sound sources. For example, when a female Glaswegian says the word "dog", all of the following sound objects (amongst others) are present, with varying degrees of prominence according to the listener's behavioural goal: the phoneme /d/, the speech token corresponding to the word 'dog', the speaker's emotional state, the speaker's gender, the speaker's individual voice, and a Glaswegian accent.

1.2.3 A working definition of auditory objects

In view of these inter-modality similarities, a working definition of auditory objects can be proposed in terms analogous to the definition of visual objects: (i) auditory objects are collections of auditory sensory data bound in a single perceptual representation and disambiguated from the auditory scene; (ii) within the same auditory sensory data, different auditory objects are present simultaneously, and may vary in prominence according to a perceiver's behavioural goals. This working definition will be employed to facilitate, both theoretically and practically, the work contained within this thesis.

1.2.4 Potential difficulties with the proposed definition of auditory objects

Useful as analogies between the objects of vision and audition may be, it is important to acknowledge their limitations. Firstly, auditory objects may be associated with different types of entities in the physical world. For example, auditory objects are often associated with a particular *source* from which sound emanates (e.g. a barking dog, a ringing telephone). However, other auditory objects may be closely identified not with a particular physical source, but with a particular acoustic *event* (e.g. a gust of wind, a thunder clap, articulation of the phoneme /d/ within a speech stream). Additionally, an auditory object may be associated with the interaction of physical entities, such that no single component of the interaction in isolation can account for the sound (e.g. the chink of a teaspoon against a porcelain cup, chalk scraping across a blackboard, footsteps on a gravel path). However, despite their differences, all of the above examples can be regarded as auditory objects according to the proposed definition. Secondly and more problematically, certain properties of auditory objects are largely modality-specific without clear equivalents in vision. For example, auditory objects generally change over time, and this temporal variation is often cognitively important (e.g., Tanaka et al., 1987). Thus, a very brief excerpt of waves lapping against a shore may be unrecognisable, whereas a longer excerpt, featuring the characteristic periodic changes in sound intensity, would be immediately identified. This raises the important issue of how to temporally delimit an auditory object. However, according to point (ii) of the proposed definition, any given excerpt of waves lapping would contain multiple wave objects of varying durations. Similarly, music is normally divisible into entities of different lengths that are present simultaneously, and all attain object status according to the current definition: e.g., in music played on a violin, the timbre, the note, the phrase, and the melody are all auditory objects. Thus, the current working definition of auditory objects suggests the inclusion of a wide array of sounds. Clearly, the proposed definition is broad; however, any more precise definition of auditory objects will require empirical identification of the collections of auditory sensory data that the brain treats as unified perceptual representations.

1.3 The physical nature of sound

This section presents a brief overview of physical acoustic properties relevant to the current studies of auditory processing.

1.3.1 Pure tones and complex sounds

Sound occurs when objects in the environment move rapidly, causing vibrations in the surrounding air. Such vibrations cause changes to the air pressure, consisting of alternating areas of compression and rarefaction; these are known as ‘sound waves’. Figure 1.3 shows a schematic of the simplest type of sound wave, a pure tone, as it travels through a particular point in space. At this point, air particles undergo repeated compressions and rarefactions (y axis), which occur regularly over time (x axis). The frequency of the pure tone is defined by the number of cycles per second, i.e. f = 1/t, where f = frequency (units of Hertz), and t = time period or the time for one cycle of vibrations (in seconds). Pure tones are therefore carriers of energy at a particular frequency. Furthermore, the given frequency determines the tone’s pitch (i.e., its place on a musical scale ordered from ‘low’ to ‘high’). Sound examples 1 and 2 are pure tones with frequencies of 200Hz and 400Hz respectively (all sound examples can be found on the CD provided inside the back cover of this thesis). Pure tones are perceptually ‘clean’ and often used in psychoacoustic experiments, but are not present in nature.

In contrast to pure tones, most of the noises we hear in the everyday world are complex sounds. Complex sounds can be defined as those that carry energy at more than one frequency simultaneously. In accord with the principles of Fourier analysis (e.g., van Drongelen, 2007) complex sounds can be regarded as the sum of many different pure tones. Complex sounds are generally described in terms of their spectral and temporal structure, i.e., the energy carried within different frequencies and at different time points respectively.

1.3.2 Spectral and temporal sound structure

Spectral and temporal aspects of sound may be conceptualized in two distinct ways. As already suggested, spectral and temporal structure can be described in terms of the energy at particular frequencies or time-points respectively. For a whole sound, the pattern of energy across different frequencies is known as the spectral shape, whilst the pattern of energy across different time-points is known as the temporal shape. Figure 1.4 shows the spectral and temporal shapes of a hammer being used (sound example 3): the temporal shape shows a distinctive pattern of energy across time, with a peak corresponding to each ‘hit, whilst the spectral shape indicates decreasing amounts of energy as the frequency level increases. In combination, temporal and spectral shapes may be represented by a spectrogram, in which time and frequency are represented along the x and y axes respectively (see Figure 1.5, and sound examples 4-7). Within a spectrogram, the amount of energy at any time-frequency combination can be indicated by the colour of the plot at the corresponding point, on a scale varying from high (hot colours) to low (cool colours). Natural sounds vary in their spectral and temporal shapes. For example, richly detailed spectral shapes are characteristic of sounds including animal vocalisations, musical instrument sounds and speech phonemes. Such sounds are said to have harmonic structure, i.e., energy at multiple regularly spaced frequency values known as harmonics, which can be seen in spectrograms as horizontal “stripes” (e.g., Figure 1.5, b and d). In contrast, sounds such as those of natural phenomena (e.g., waves, rain, wind), machinery, tools and engines have little harmonic structure and instead consist of auditory noise: they contain energy at frequencies across a wide range and thus lack rich spectral detail (e.g., Figure 1.5, a and c). Natural sounds also vary in their temporal shapes, either containing distinctive temporal patterns (rhythmicity, e.g., Figure 1.5, a and c) or remaining relatively constant across time (e.g., Figure 1.5, b and d).

The relative influence of spectral and temporal shapes upon sound identity varies for different natural sounds. For example, the sound of a telephone ring is primarily dependent upon temporal shape, and may be recognised despite radical changes in spectral shape; in contrast, individual voices are distinguished by their particular spectral shapes, and may be identified despite

the articulation of words with contrasting temporal shapes (see Figure 1.6, and sound examples 8-11).

Spectral and temporal aspects of sound can alternatively be conceptualised in terms of the fluctuations of energy content across the frequency range and across time; these characteristics are known as spectral and temporal modulations respectively. Multiple different spectral and temporal modulations often occur simultaneously within the same sound, at different rates (or resolutions) ranging from slow to fast (temporally), and from narrow to broad frequency ranges (spectrally). Furthermore, just as complex sounds can be broken down into constituent pure tones, they can also be broken down into constituent spectral and temporal modulations (e.g., Woolley et al., 2005; Elliott and Theunissen, 2009). These basic modulation units, known as 'ripples', exist for every temporal and spectral rate, and together provide a 'multi-resolution' representation of sound (Singh and Theunissen, 2003; Chi et al., 2005). Certain categories of natural sounds tend to feature distinctive combinations of particular temporal and spectral ripples (Singh and Theunissen, 2003). For example, animal vocalisations (including human speech) contain high spectral modulation rates concentrated at low temporal modulation rates, whilst environmental sounds tend to contain low spectral modulation rates at low temporal modulation rates (Singh and Theunissen, 2003; Woolley et al., 2005). From this perspective, the conjunction of spectral and temporal structure is an important determinant of sound identity (in addition to spectral and temporal features considered separately), and real world sounds are properly considered 'spectrotemporal' entities. The stereotypical spectrotemporal structures associated with particular types of sounds are often referred to as spectrotemporal 'signatures'.

1.3.3 Pitch

Pitch is the auditory property that allows sounds to be ordered on a musical scale from 'low' to 'high', and can be evoked by both pure tones and complex sounds (e.g., Wang and Bendor, 2010). Pitch is a percept, defined psychoacoustically rather than physically, since the same pitch can be evoked by a range of physically different stimuli. There are at least two types of acoustic

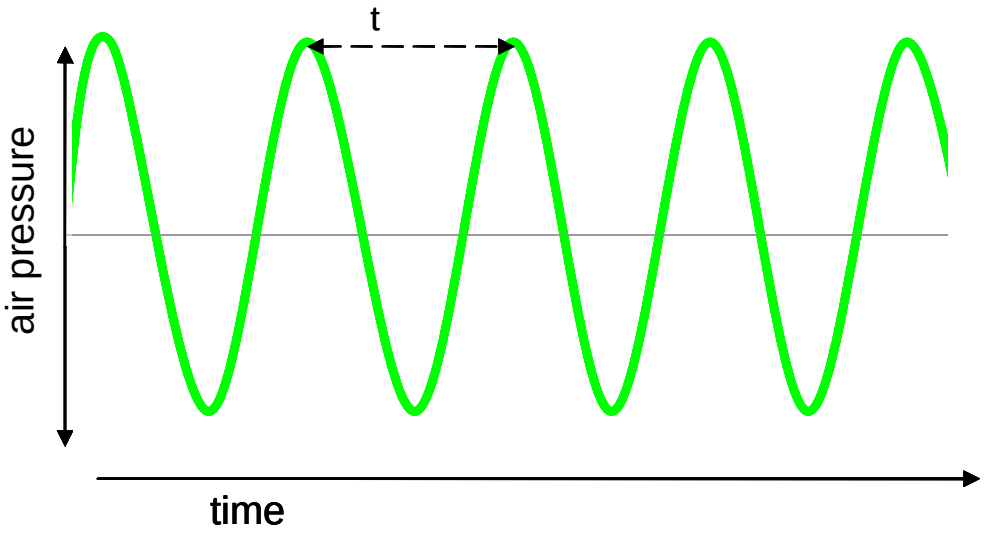
information from which pitch percepts can be extracted; either or both may be used in different contexts. Firstly, pitch may be evoked by temporal information, based upon the regular repetition rate of acoustic energy over time. Alternatively, pitch may be perceived spectrally, as the fundamental frequency (f0) of a complex sound. The fundamental frequency is the highest frequency for which each harmonic component in a complex sound is an integer multiple; additionally, the fundamental frequency is also equal to the frequency spacing between consecutive harmonics. In practice, this means that a sound consisting of harmonics at 50, 100, 150, and 200Hz would have a fundamental frequency (and perceived pitch) of 50Hz. An important point about fundamental frequency is that even when it is not physically present in a sound the pitch percept remains the same. Thus, combined harmonics at 100, 150, and 200Hz would still evoke a pitch of 50Hz; this phenomenon is known as missing fundamental pitch.

1.3.4 Timbre

Like pitch, timbre is a psychoacoustically defined percept rather than a physical sound property. Timbre is the auditory property that distinguishes two sounds of identical pitch, loudness and duration; perceptually, it might be equated loosely with sound ‘quality’ or ‘colour’ (the auditory distinction between a flute and a clarinet playing the same note, or two human voices of the same gender speaking the same word). Timbre is generally a perceptually stable property (for example, it is preserved under large shifts of pitch when a solo instrument plays a melody), and therefore serves an important role in the tracking and disambiguation of particular sound sources in natural auditory scenes. Spectral and temporal sound structures (whether conceptualised in terms of shapes or modulations) are key influences upon timbre. For example, the distinction between a flute and a clarinet is predominantly based upon contrasting spectral shapes (harmonic structures), whilst the distinction between a violin and a piano is based upon contrasting temporal shapes (violin notes feature a relatively gradual building up of energy, whilst piano notes are characterised by more rapid onsets). In many sounds, timbre is constituted by a complex combination of spectral and temporal properties, i.e., spectrotemporal structure. Furthermore, the timbres of particular objects may consist of characteristic

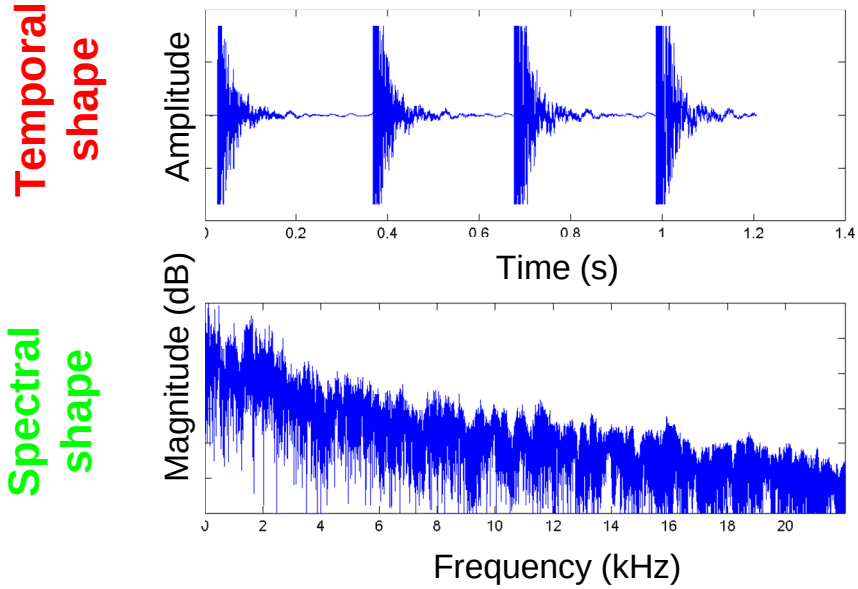
spectrotemporal signatures. Thus, timbre may be conceptualised as a multi-dimensional spectrotemporal property that cannot be ordered along a single perceptual scale like pitch.

Figure 1.3 Schematic of a pure tone



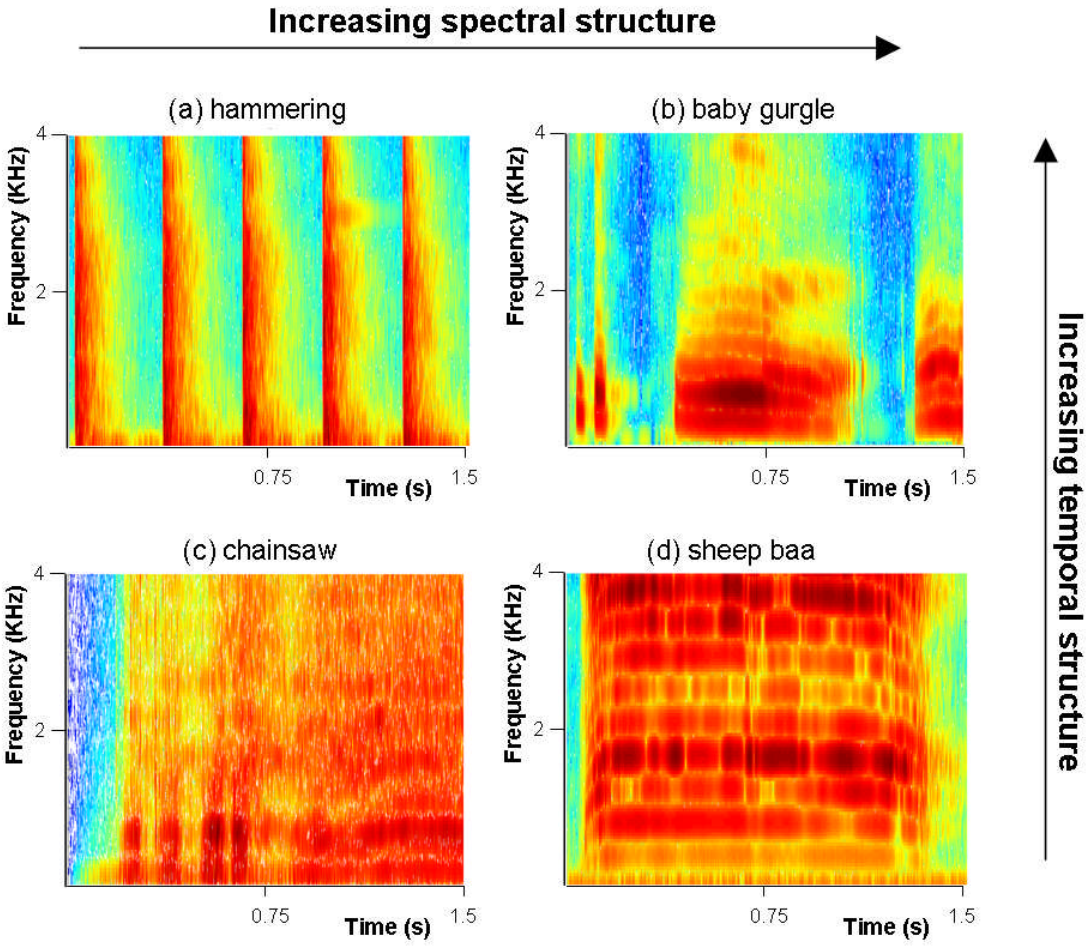
Pure tone depicted in green. KEY: t, time period, i.e., the time for one cycle of vibrations (see section 1.3.1 and sound examples 1-2).

Figure 1.4 Spectral and temporal shapes of the sound of a hammer being used



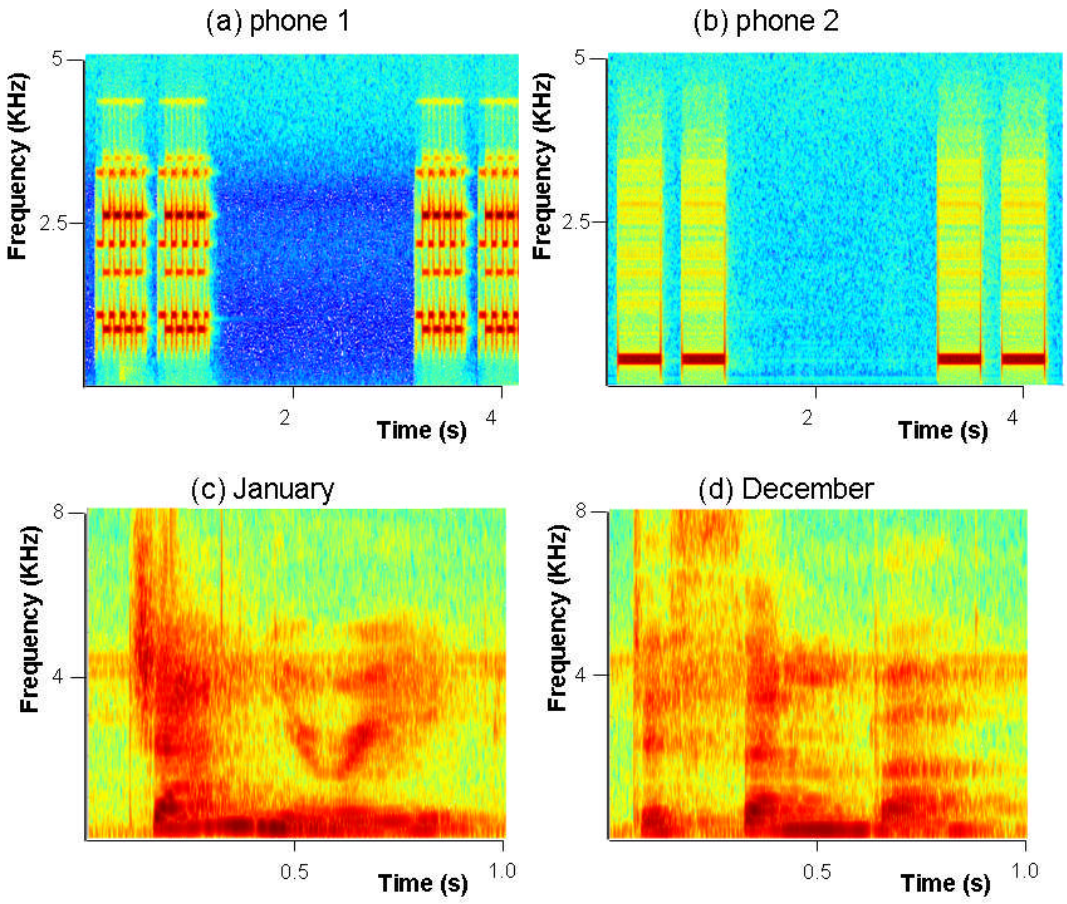
See text for details (section 1.3.2 and sound example 3)

Figure 1.5 Spectrograms of four natural sounds, illustrating variations in spectral and temporal structure



See text for details (section 1.3.2 and sound examples 4-7)

Figure 1.6 Spectrograms illustrating the maintenance of sound identity despite radical alterations in either spectral or temporal structure



Panels (a) and (b) show the spectrograms of two different telephones ringing; here, the semantic message is maintained despite radical alterations in spectral shape, suggesting that recognition in this case is predominantly dependent upon temporal information. Panels (c) and (d) show the spectrograms of two words ('January', 'December'), spoken by the same individual; here, vocal identity is maintained despite radical variations in temporal structure, suggesting that voice recognition may rely upon the analysis of spectral shape. See also section 1.3.2 and sound examples 8-11.

1.4 Foci of current investigations

This thesis will focus upon four broad levels of cortical non-verbal auditory processing, all of which involve the processing of non-isomorphic representations predominantly in cortical (rather than sub-cortical) substrates. The first level focuses upon the processing of relatively simple auditory perceptual properties. The remaining three levels are concerned with the processing of auditory objects, i.e., collections of auditory perceptual properties bound in unified cognitive representations corresponding to single entities in the world. All four levels of processing are defined in more detail below.

In the visual neuropsychological literature, the term ‘agnosia’ is used to describe deficits of object processing (in the absence of blindness). By extension, the term auditory agnosia has been adopted to mean any deficit of auditory object processing (in the absence of deafness; Griffiths et al., 1999), although it remains rather loosely defined and has been used to refer to different types of disorders by different authors (Simons and Lambon Ralph, 1999). For clarity in what follows, precise terminology will be employed to distinguish the different forms of auditory agnosia; these are also defined below.

1.4.1 Perceptual property processing

Perceptual property processing involves the cortical analysis of perceptual properties which contribute to, but are unlikely in themselves to constitute, whole object representations. Examples of auditory perceptual properties include frequency, pitch, and timbre. In general, there is a lack of formal terminology to describe perceptual property processing deficits; however, the term ‘dystimbria’ refers to an impairment of timbre processing.

1.4.2 Apperceptive object processing

Apperceptive processing refers to the perceptual representation of whole auditory objects, analogous to the apperceptive level of visual object processing (e.g., Warrington and Taylor, 1978; Riddoch and Humphreys, 1987). Corresponding deficits are indicated by the term ‘auditory apperceptive agnosia’.

1.4.3 Semantic object processing

Semantic (or associative) processing refers to the association of stored knowledge, or semantic memory, with perceptual (apperceptive) object representations. Corresponding deficits are indicated by the term ‘auditory associative agnosia’.

1.4.4 Auditory scene analysis

Auditory scene analysis (ASA) refers to the collection of cognitive processes by which the auditory scene is parsed into discrete sound objects (Bregman, 1990). There is currently a lack of terminology to describe deficits of ASA.

1.5 A review of the neuropsychological literature of non-verbal auditory cortical processing deficits

The following discussion will review neuropsychological deficits corresponding to each of the four broad levels of cortical non-verbal auditory processes upon which this thesis will focus (perceptual property, apperceptive and semantic processing, and auditory scene analysis). Additionally, one further auditory processing deficit that is not a target for investigation, cerebral deafness, will be briefly described. In view of the planned neuropsychological investigations, this literature review will emphasise neuropsychological evidence; however, insight from other methodologies including functional imaging studies of healthy humans and electrophysiological recordings in animals will also be described where relevant.

1.5.1 Cerebral deafness

Cerebral deafness (also known as cortical deafness) involves a near complete loss of sound perception following cerebral damage. This syndrome typically follows bilateral damage involving primary auditory cortex and/or its sub-cortical connections (Griffiths et al., 1999). Since patients sometimes make variable responses to auditory stimuli, it has been suggested that the syndrome may have an attentional component; however, even when attention is taken into account a hearing loss remains, suggesting the simultaneous presence of a cerebral auditory perceptual deficit (Tanaka et al., 1987). However, cerebral deafness is rare, and furthermore, is particularly unlikely in dementia given the prevalence of cortical (over sub-cortical) degeneration. Finally, since hearing loss in cerebral deafness is typically severe and highly debilitating, patients with this syndrome would be unsuitable for neuropsychological investigations of non-verbal auditory object processing. Thus, cerebral deafness will not be discussed in this thesis any further.

1.5.2 Perceptual property processing deficits

Perceptual property processing involves the analysis of perceptual properties which contribute to, but are unlikely in themselves to constitute, object

representations. Thus, auditory perceptual property processing includes the representation of individual properties like pitch and timbre, but not whole sound objects. Implicated brain mechanisms are predominantly cortical, and involve the processing of 'perceptual' representations, i.e., those that do not code physical structure directly, but that emphasize perceptually relevant properties. Evidence suggests that the analysis of different types of auditory properties relies upon distinct cortical processes, and thus property perception is unlikely to be a unitary stage of cognition. In what follows, neuropsychological deficits corresponding to the processing of three perceptual properties, pitch, timbre, and auditory size, will be discussed.

1.5.2.1 Pitch processing deficits

1.5.2.1.1 Pitch processing deficits: neuropsychological evidence

The auditory property of pitch is defined in section 1.3.3. In neuropsychology, pitch processing is commonly assessed by presenting two sequential sounds and asking subjects to either detect or discriminate the direction of a pitch-change. In studies of patients with brain damage, impaired pitch-change detection has been associated with involvement of both sub-cortical structures and the primary auditory cortex (Habib et al., 1995; Tramo et al., 2002; Hattiangadi et al., 2005; Terao et al., 2006). In contrast, impaired pitch-change direction discrimination is generally associated with cortical areas in secondary auditory cortex (lateral Heschl's Gyrus; Lechevalier et al., 1984; Tanaka et al., 1987; Tramo et al., 2002; Terao et al., 2006; for a comprehensive review, see Stewart et al., 2006). Evidence from temporal lobectomy groups, in studies using both pure tones (Johnsrude et al., 2000) and complex sounds (Zatorre, 1988), is convergent with this picture: pitch-change discrimination deficits are associated with resection of secondary auditory cortex, and are particularly severe with involvement of the right hemisphere. The latter study by Zatorre and colleagues (1988) is particularly suggestive of a cortical processing problem because participants were forced to rely upon perceptual rather than physically-based pitch representations via the use of 'missing fundamental' stimuli (i.e., sounds with no energy at the fundamental frequency, see section 1.3.3). Together, these findings suggest that pitch-change detection and discrimination

are anatomically dissociable: whilst detection is associated with areas of the auditory pathway prior to and including primary auditory cortex, direction tasks are associated with secondary auditory cortex. Additionally, the anatomical associations of these results may suggest that pitch-change detection predominantly depends upon isomorphic representations of physical properties (like frequency) in sub-cortical regions, whereas pitch-change direction discrimination involves more complex cortical representations, encoding elements beyond the physical properties of stimuli.

Neurological deficits of pitch processing might be compared to congenital amusia, which is a developmental disorder characterised by lifelong difficulty in perceiving pitch changes (Stewart et al., 2006). In concordance with the neurological cases described above, past studies of congenital amusia have emphasised abnormal pitch-change detection and direction discrimination, but with the most striking impairments for direction discrimination (Foxton et al., 2004; Hyde and Peretz, 2004; Stewart et al., 2006). However, whilst earlier studies of amusic subjects emphasise a property processing deficit that particularly affects the perception of pitch (e.g. Foxton et al., 2004), more recent investigations highlight the involvement of further cognitive processes including memory and attention. For example, research indicates that individuals with congenital amusia suffer short term memory deficits that affect the processing of a range of auditory properties including pitch (Williamson et al., 2010b), timbre (Tillmann et al., 2009) and prosody in speech (Liu et al., 2010), but not verbal sound objects such as words and digits (Tillmann et al., 2009; Williamson and Stewart, 2010). Additionally, the amusic brain shows abnormal structural morphology and functional responses in the inferior frontal cortex and its connections, thus implicating attentional mechanisms in observed deficits (Hyde et al., 2007; Peretz et al., 2009; Hyde et al., 2010). Finally, it has been suggested that amusic subjects might show weak or absent long term memory (i.e., stored knowledge) for musical structure, which would ordinarily support pitch analysis (Williamson and Stewart, 2010). Taken together, emerging evidence from studies of amusia suggest a close association between perceptual property processing, with a particular emphasis upon pitch, and executive mechanisms (for short and long term memory, and attention). Thus, data are consistent with a pitch-specific fronto-temporal network, involving close

associations between brain regions implicated in both auditory perceptual and executive processes. If this assertion is correct, pitch perception deficits might be predicted in dementia syndromes involving selective damage to similar fronto-temporal networks, such as PNFA and LPA.

1.5.2.1.2 Pitch processing: studies of healthy controls

Neuropsychological associations between pitch processing and the secondary auditory cortex (lateral Heschl's gyrus) are consistent with functional imaging studies of the normal brain. Such studies have exploited the fact that the pitch percept evoked by a sound is dissociable from its physical structure; this dissociation allows the changes in neural activity associated with pitch to be attributed to perceptual, rather than physical, stimulus differences. For example, whilst random noise sounds ordinarily have no pitch, the regular temporal repetition of such sounds evokes the perception of a pitch at the repetition frequency; such stimuli are referred to as Iterated Ripple Noise (IRN, see Griffiths et al., 1998; Patterson et al., 2002). By contrasting IRN and physically matched random noise stimuli, Patterson et al. (2002), have provided evidence for a pitch-processing 'centre' in secondary auditory cortex bilaterally. Notably, this finding is supported by a number of other studies that have adopted a similar approach with contrasting types of pitch-evoking stimuli (e.g., Penagos et al., 2004; Gutschalk et al., 2004; Schneider et al., 2005). For example, Penagos et al. (2004) manipulated pitch salience (by varying the resolved and unresolved harmonic content of sounds) but controlled for physical differences, and revealed an association between pitch salience and processing in secondary auditory cortex. Furthermore, Schneider et al. (2005) examined individual differences in pitch perception using missing fundamental tones, and found a correlation between the type of pitch perception adopted and both structural and functional asymmetry in secondary auditory cortex. These findings are also corroborated by primate studies that suggest the presence of a pitch centre in a homologous cortical region (Bendor and Wang, 2005). More recent evidence, however, suggests that multiple cortical pitch-processing centres may exist, corresponding to the analysis of different types of pitch-evoking stimuli. According to this view, regions would include but extend beyond secondary auditory cortex, perhaps encompassing the temporo-parieto-

occipital junction and/or prefrontal cortex (Hall and Plack, 2009); furthermore, such conclusions would be convergent with the evidence from amusia, which indicates the influence of a distributed fronto-temporal network.

1.5.2.1.3 Pitch processing: section summary

Overall, the neuropsychological literature suggests an association between pitch-direction discrimination and cortical processing in right secondary auditory cortex (lateral Heschl's gyrus). Corresponding data from functional imaging studies of healthy humans are broadly convergent with this picture, nominating secondary auditory cortex bilaterally as a pitch processing centre. However, more recent studies in both congenital amusia and healthy subjects suggest the additional involvement of executive processes, and further regions throughout the temporal, parietal, and frontal lobes. Such evidence might indicate the action of a relatively pitch-specific fronto-temporal network, involving close associations between regions for auditory perceptual and executive processing.

1.5.2.1.4 Pitch processing deficits in dementia

Indirect anatomical evidence suggests that patients with dementia might show relatively intact pitch processing mechanisms. Specifically, the syndromes of PPA and AD typically cause damage within auditory association cortices but leave areas implicated in pitch processing (primary and secondary auditory cortices) relatively intact (Dekosky and Lopez, 2007; Kipps and Hodges, 2007). Indeed, although pitch processing has been rarely investigated in dementia, one study describes relatively preserved pitch perception in patients with AD (Kurlyo et al., 1993). However, dementia syndromes also involve varying atrophy beyond the auditory cortices, in regions that may overlap with pitch-specific fronto-temporal processing networks; thus, dementia might involve deficits of pitch perception that are closely associated with non-auditory executive processing impairments. Present investigations will probe pitch processing deficits in a range of dementia syndromes (SD, PNFA, LPA, AD); given that these syndromes involve anatomically distinct profiles of distributed atrophy, the comparison of syndrome-specific pitch processing deficits may help to illuminate the cortical organization of corresponding functional networks.

1.5.2.2 Timbre processing deficits

1.5.2.2.1 Timbre processing deficits: neuropsychological evidence

The auditory property of timbre is defined in section 1.3.2. Neuropsychological studies have described selective impairments of timbre perception ('dystimbria') following focal damage to the auditory association cortices of the posterior superior temporal lobe, particularly with involvement of the right hemisphere (Mazzucchi et al., 1982; Griffiths et al., 2007). For example, Mazzucchi et al. (1982), described a patient who, following a stroke, was unable to discriminate between sounds with similar timbres (such as voices or vehicle engine notes), but able to recognise other environmental sounds (reportedly using rhythm or pitch cues); however, no rigorous psychoacoustic assessments were made to support these qualitative descriptions. In further studies, the selective preservation of timbre processing has also been reported: Peretz et al. (1994) reported a further stroke patient who could discriminate instrumental timbres carrying a melody, but not the melody itself. Furthermore, whilst this patient had incurred damage to the bilateral primary auditory cortices, the right auditory association cortices were spared. Taken together, such evidence may tentatively indicate that timbre processing is a relatively independent stage of auditory cognition.

Whilst these studies support the existence of selective timbre impairments generally, further studies have attempted to determine the relative contributions of spectral, temporal and spectrotemporal mechanisms, all of which might be relevant to timbre perception. Griffiths et al. (2007) described a patient who, following a stroke, perceived a 'mechanical' quality in natural sounds such as birdsong, and had particular difficulty discriminating between sounds dependent upon timbral cues. In formal psychoacoustic assessments using synthetic timbre stimuli, this patient was unable to discriminate spectral shapes but could discriminate both temporal shapes and pitch normally. This deficit of spectral processing was associated with right-sided damage to the temporal lobes, including primary, secondary and posterior auditory association cortices (including the planum temporale). In contrast, a further case report of a stroke

patient (Kohlmetz et al., 2003) has emphasized deficits of spectrotemporal analysis in dystimbria. Here, the patient was unable to discriminate between musical instruments that produce notes with abrupt onsets (e.g. percussion, keyboards); such discriminations require spectrotemporal analysis of spectral shapes across very short temporal windows, i.e. “rapid spectral analysis”. However, the patient remained able to discriminate between musical timbres more reliant upon purely spectral timbre cues, such as those of wind instruments. This deficit of spectrotemporal processing was associated with damage to right-lateralised regions including auditory association cortices, as well as the middle temporal lobe and insula. Additionally, lesion-led studies in patients following anterior temporal lobectomy have attempted to describe the spectral and temporal deficits underlying dystimbria (Samson and Zatorre, 1994; Samson et al., 2002). Samson and colleagues (2002) assessed patients with spectrally and temporally varying synthetic timbre stimuli, and reported both spectral and temporal deficits in right and left temporal lobe excision groups; however, the right hemisphere group were generally more impaired, and showed particularly severe deficits for temporal rather than spectral processing. Finally, there is a small literature detailing the impairment of temporal property processes that are likely to be implicated in timbre analysis, typically following bilateral damage to the primary auditory cortex (although anatomical substrates vary; Albert and Bear, 1974; Auerbach et al., 1982; Miceli, 1982; Tanaka et al., 1987; Yaqub et al., 1988; Buchtel and Stewart, 1989; Otsuki et al., 1998). Such patients present with prominent word perception difficulties, and are therefore diagnosed with the syndrome of ‘word deafness’ (for further discussion see section 1.6.3.3). However, detailed examinations of these cases suggest that word deafness symptoms are secondary to observed temporal processing deficits; for example, patients are unable to distinguish simple sounds presented in quick succession (e.g., pairs of noise bursts), and instead perceptually ‘fuse’ multiple stimuli into a single object (e.g., Albert and Bear, 1974; Auerbach et al., 1982). Such deficits of temporal resolution might be regarded a form of dystimbria; however, the explicit examination of timbre analysis has yet to be conducted in this group.

Taken together, the neuropsychological literature suggests the existence of a heterogeneous range of selective timbre processing impairments that reflect

either spectral, temporal or spectrotemporal perceptual deficits. Evidence for impairments chiefly affecting one of these three processes attests to their cognitive independence. The anatomical evidence for dystimbria appears somewhat conflicting; however, neuropsychological studies tend to emphasise right-lateralised damage, and lesion studies suggest a prominent role for right posterior auditory association cortices. Whilst the lack of a clear anatomical association might reflect the relatively gross brain damage evident in most cases, it might equally suggest that timbre processing depends upon a combination of spectral, temporal and spectrotemporal mechanisms distributed throughout partially overlapping regions of the auditory cortices.

1.5.2.2.2 Timbre processing: studies of healthy subjects

There is substantial convergence between neuropsychological studies of dystimbria and evidence provided by functional imaging studies of healthy subjects. For example, a direct examination of timbre perception using fMRI (functional Magnetic Resonance Imaging) showed greater right than left activation throughout primary and auditory association cortices (Halpern et al., 2004). Additionally, this study examined the conjunction of timbre perception and timbre imagery (i.e., imagining currently absent timbre sounds), which is more likely to reflect the representation of timbre percepts rather than any associated physical characteristics: this revealed activation only in bilateral posterior auditory association cortices of the superior temporal sulcus (STS) including the planum temporale (PT). Further studies have sought to describe substrates corresponding to the spectral, temporal or spectrotemporal processes that are likely to underlie timbre processing. For example, Warren et al. (2005a) used fMRI to observe anatomical correlates of spectral shape processing, and revealed activity within right auditory association cortices (STS) and bilateral PT. Further fMRI studies have provided evidence for a degree of independence between spectral and temporal mechanisms; although these are both likely to rely on bilateral substrates, evidence suggests that they show relative lateralisation to right and left auditory cortical regions respectively (including primary, secondary and auditory association areas; Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010). Other authors have suggested that such lateralisation of function may alternatively reflect auditory

processing within time windows of varying duration (longer and shorter for spectral and temporal processes respectively; Poeppel, 2003; Boemio et al., 2005); however, irrespective of the preferred theoretical interpretation, such findings provide an anatomical account of relatively independent sub-processes of timbre perception. Additionally, further examination of these results suggests that spectral and temporal mechanisms show only a partial dissociation, since they overlap considerably within regions of bilateral auditory association cortices (Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010); such findings might indicate the additional presence of spectrotemporal mechanisms, and indeed, direct support for this claim in a region of left posterior auditory association cortex has been recently provided (Altmann et al., 2010). This work in healthy human subjects is supported by electrophysiological recordings in animal auditory cortices, which indicate the topographical mapping of spectral, temporal, and conjoint spectrotemporal modulation rates in homologous substrates (Kowalski et al., 1996; Depireux et al., 2001). Taken together, the neuroimaging of healthy subjects emphasises the role of bilateral auditory association cortices in timbre processing. However, the topography of results suggests that spectral and temporal sub-processes may be predominantly conducted within right and left auditory cortices respectively, whilst spectrotemporal representation may occur within posterior auditory association cortices. In view of these conclusions, it might be proposed that timbre analysis depends upon a distributed network traversing a range of bilateral primary, secondary and auditory association regions, culminating in full spectrotemporal timbre representations in posterior regions of the superior temporal sulcus. Indeed, this conclusion is supported by computational and connectivity-based studies of timbre (spectral) processing, which suggest that timbre processing depends upon interactions between primary auditory cortex and PT (Kumar et al., 2007; Griffiths et al., 2007).

This body of functional neuroimaging work is convergent with corresponding neuropsychological evidence. For example, the observation of patients with relatively selective spectral, temporal and spectrotemporal deficits corresponds to the anatomical dissociation of these processes in healthy subjects. Additionally, the absence of a clear anatomical correlate for dystimbria in the neuropsychological literature would be explained if timbre analysis depends

upon a distributed network traversing a range of auditory regions. However, given the lateralization of spectral and temporal functions in healthy subjects, the emphasis upon right-sided damage in dystimbria might indicate that timbre processing is often heavily reliant upon spectral analysis.

1.5.2.2.3 Timbre processing: section summary

Neuropsychological results suggest that timbre analysis is dissociable from other mechanisms of non-verbal sound processing. Both neuroimaging and neuropsychological studies indicate that timbre discrimination can be divided into relatively independent spectral, temporal, and spectrotemporal mechanisms. However, given the considerable overlap between spectral, temporal and spectrotemporal mechanisms both in healthy and damaged brains, timbre processing is likely to rely upon a distributed network traversing regions throughout bilateral auditory cortices. Finally, an emphasis upon the role of posterior auditory association cortices may suggest the particular involvement of this region in the representation of full spectrotemporal timbre percepts.

1.5.2.2.4 Timbre processing deficits in dementia

Deficits of timbre perception have been rarely investigated in dementia, although one group study details a timbre deficit in patients with AD (Kurylo et al., 1993). However, in view of the above evidence, dystimbria but might be predicted in a variety of dementia syndromes involving atrophy of the auditory cortices, and in particular, the posterior auditory association cortices. Thus, present investigations will examine timbre processing in a range of relevant dementia syndromes (SD, PNFA, LPA, AD); given that these syndromes involve anatomically distinct profiles of distributed atrophy, the comparison of syndrome-specific timbre processing deficits may help to illuminate the cortical organization of corresponding functional networks.

1.5.2.3 Auditory size processing deficits

1.5.2.3.1 An introduction to size processing

Processing the size of sound sources is a fundamental task of auditory perception: it both provides behaviourally important information about the source, and enables normalization for the acoustic effects of size during perceptual processing (Smith et al., 2005). Indeed, humans effortlessly perceive the size of many sound sources, including other human speakers (Smith et al., 2005; Smith and Patterson, 2005), and musical instruments (van Dinther and Patterson, 2006). Perceived acoustic size is dependent upon the length of the resonant tract through which a sound is emitted (e.g., the vocal tract in the case of human speakers). As a sound moves through the length of an empty space, it is filtered such that energy at the space's resonant frequencies is amplified, and energy at other frequencies is attenuated. This has the effect of altering both spectral and temporal shape (i.e. timbre), to reflect the space's length, which in living animals and musical instruments is associated with the sound source's size. For example, shorter vocal tract lengths result in an upward shift of spectral shape towards higher frequencies, and a compression of temporal shape (i.e., shorter sound decay times), thus producing the percept of a smaller individual (von Kriegstein et al., 2006; von Kriegstein et al., 2007). These modifications are independent of pitch, which may remain constant whilst perceived size is altered.

1.5.2.3.2 Size processing: studies of healthy controls

Imaging studies of healthy subjects implicate both sub-cortical and cortical structures in the processing of auditory size. Sub-cortically, evidence indicates that the medial geniculate body (MGB) in the ascending auditory pathway represents basic (isomorphic) size cues independently of related acoustic parameters such as pitch (von Kriegstein et al., 2006). Cortically, size processing is likely to rely both on the intraparietal sulcus to process representations of relative magnitude, and anterior regions of the superior temporal gyrus (STG) to support the audio-visual matching of sound sources with their physical appearances (von Kriegstein et al., 2006; von Kriegstein et al., 2007). Additionally, the left posterior STG, including the planum temporale (PT), is selectively engaged during the size processing of speech but not other

sound categories (von Kriegstein et al., 2007). It is suggested that this selectivity for speech may reflect an increased requirement during verbal communication to ‘normalize’ for acoustic size, i.e., to disambiguate the perceptual changes that reflect size from those that reflect particular speech tokens (it is unlikely that normalization processes are required to the same degree during the processing of other sound categories; von Kriegstein et al., 2007). Finally, electrophysiological work in gerbils trained to discriminate human vowels (Schebesch et al., 2010), provides additional evidence for a cortical substrate that represents the size of verbal sounds independently of other acoustic parameters.

1.5.2.3.3 Size processing deficits in dementia

The relative preservation of sub-cortical structures in dementia suggests that patients may show preserved perception of basic auditory size cues. However, particular dementia syndromes involving temporal and parietal atrophy might lead to more complex deficits of size processing, such as relative magnitude representation, audio-visual matching, and perceptual normalization. To date, no investigations of size processing have been conducted in dementia or other neurological populations; thus, present investigations will include a preliminary assessment of size processing in a range of distinct dementia syndromes, in an effort to illuminate the cognitive processes and cortical networks involved.

1.5.3 Apperceptive processing deficits

1.5.3.1 An introduction to apperceptive processing deficits

The term apperceptive processing refers to mechanisms that enable the perceptual representation of whole objects, prior to the attribution of meaning. Since objects are formed from particular collections of perceptual properties, apperceptive processing is likely to involve the allocation, or matching, of property representations to stored object representations. In the visual neuropsychological literature, evidence for an independent stage of apperception is provided by reports of patients with selective visual apperceptive deficits. Specifically, a rich literature describes the syndrome of

‘visual apperceptive agnosia’ which involves impaired object identification under non-canonical viewing conditions, or impaired perceptual matching of object representations, despite demonstrably intact processing of basic visual properties (Taylor and Warrington, 1971; Warrington and Taylor, 1973; Warrington and Taylor, 1978; Warrington and James, 1986; Riddoch and Humphreys, 1987; Warrington and James, 1988; Riddoch et al., 2008). For example, whilst patients are able to identify clearly presented and familiar objects, they are unable to match different exemplars of the same object viewed from different angles, or to identify objects presented against complex backgrounds. Additionally, the selectivity of visual apperceptive deficits is further supported by evidence that they tend to follow relatively circumscribed anatomical damage to the right parietal lobe (Warrington and Taylor, 1973; Warrington and James, 1988). Although theoretical accounts differ, it is commonly suggested that visual apperceptive agnosia reflects an inability to match perceptual properties to stored ‘structural’ object representations; in particular, these are held to specify the volumetric and geometric structure of objects in a manner that is invariant to perspective or viewing context (Warrington and James, 1986; Riddoch and Humphreys, 1987). For example, the structural representation of a mug would combine information about its volumetric shape (cylindrical) and its features (handle, closed at one end). From first principles, the process of matching perceptual properties to structural representations is likely to be a computationally demanding task because the perceptual properties of objects are often distorted by contextual factors and are therefore widely variable; e.g., the same visual object may be presented from radically different perspectives, or under different lighting conditions. From this perspective, apperceptive processing is likely to involve mechanisms of ‘object invariance’ which enable the association of physically variant properties with consistent structural object representations; such mechanisms would facilitate the recognition of perceptually variant mugs (i.e., of different sizes, proportions, colours, materials etc.) from any perspective. Taken together, observations of visual apperceptive agnosia have led researchers to argue that visual cognition involves an independent stage of apperception or object invariance, which is dependent upon processing in the right parietal lobe.

Whether or not auditory object cognition, like visual object cognition, is reliant upon a discrete stage of apperception is a matter of debate. In the visual modality, it is plausible that a 'library' of stored structural descriptions would enable the recognition of a wide range of objects under altered viewing conditions. In the auditory modality, it has been suggested that broadly analogous structural descriptions, known as 'auditory templates', might specify the typical spectrotemporal characteristics of common objects in a relatively abstract code, to enable recognition under altered listening conditions (Griffiths and Warren, 2002). For example, auditory templates of phonemes might facilitate the interpretation of words spoken with different accents or by different speakers, and auditory templates of melodies would allow the recognition of tunes played on different instruments. More generally, auditory templates might provide a mechanism for detecting auditory objects within noisy environments, i.e., auditory scene analysis (ASA; Bregman, 1990; see section 1.5.4.1). Despite these suggestions, it is as yet unclear whether mechanisms of apperceptive processing are as pervasive in the auditory as in the visual modality. Firstly, individual exemplars corresponding to one object may be inherently more variable in the auditory than the visual modality (consider the perceptual range of sounds corresponding to cat vocalisations, or a person using a spade); from this perspective, auditory apperceptive processing would require mechanisms for mapping highly variable exemplars onto a single and relatively abstract structural representation. Secondly, the existence of auditory apperceptive agnosia, and thus a discrete stage of auditory apperception, is only partially supported by the neuropsychological literature. Although several studies suggest the presence of this syndrome, many suffer from a lack of rigorous cognitive testing and the imprecise use of terminology; thus it is often unclear whether patients suffer property, apperceptive or associative processing impairments. Adhering to the analogous definition in the visual modality, auditory apperceptive agnosia would involve impaired object identification under non-canonical perceptual conditions, or impaired perceptual matching of object representations, despite demonstrably intact property processing mechanisms. However, adequate reports of auditory apperceptive agnosia suggest that it is often accompanied by property processing deficits (Albert and Bear, 1974; Auerbach et al., 1982; Griffiths et al., 1997; Wang et al., 2000; Stefanatos et al., 2005; Saygin et al., 2010). Given that auditory cognition is held to involve, to

some extent, the serial processing of increasingly complex representations (Rauschecker, 1998; Binder et al., 2000; Wessinger et al., 2001; Griffiths and Warren, 2004), observed apperceptive impairments might be secondary to primary property processing deficits. Additionally, there is no clear anatomical substrate corresponding to auditory apperceptive deficits, although damage tends to involve the primary and/or association auditory cortices bilaterally, and their connections (Griffiths et al., 1999). Nevertheless, a detailed analysis of purported auditory apperceptive agnosia cases suggests that parallel property processing deficits tend to be fine-grained, often affecting only restricted categories of sound objects (e.g., words, environmental sounds, music). Furthermore, it can be argued that these patients show apperceptive impairments that are disproportionately severe compared to their accompanying property processing deficits (Griffiths et al., 1997; Wang et al., 2000; Stefanatos et al., 2005; Saygin et al., 2010). In view of this evidence, it may be suggested that subtle property processing deficits combine in a non-linear fashion to cause predominantly apperceptive disorders for particular categories of sound. Thus, preliminary evidence supports the existence of auditory apperceptive deficits, and corresponding mechanisms of apperception, although it also indicates that such mechanisms may differ considerably between the auditory and visual modalities. For example, since auditory apperceptive deficits appear less selective, both cognitively and anatomically, auditory object apperception may be more dependent upon other processes such as property perception or the top-down application of semantic knowledge. However, further data, particularly from rigorous neuropsychological investigations, is required to examine these hypotheses in detail. To facilitate such studies within this thesis, auditory apperceptive agnosia will be operationally defined as a perceptual object processing deficit that is disproportionately severe in comparison to any accompanying impairments of property processing; notably, this definition would exclude patients with relatively broad property processing deficits that disable the perception of all sounds, but would include patients with fine-grained property processing deficits that affect only restricted categories.

1.5.3.2 Auditory apperceptive deficits: behavioural evidence

Following the above definition, the neuropsychological literature provides some evidence for relatively selective deficits of auditory apperceptive processing. For example, both behavioural and anatomical studies have supported a dissociation of apperceptive from associative (semantic) auditory agnosia (Eustache et al., 1990; Schnider et al., 1994; Vignolo, 2003). Additionally, behavioural investigations have described a number of single cases with predominant object processing deficits who show perceptual rather than semantic errors during sound identification tests, suggesting the presence of apperceptive rather than associative disorders (e.g. Mendez and Geehan, 1988; Fujii et al., 1990; Habib et al., 1995). Furthermore, a range of single case studies have employed psychoacoustic measures to provide evidence for the cognitive mechanisms underlying apperceptive impairments (e.g., Wang et al., 2000; Saygin et al., 2010); these studies will be discussed in detail below. Taken together, the neuropsychological literature supports the existence of a relatively independent stage of cognition corresponding to the apperceptive processing of auditory objects.

Further analyses of the literature suggest that auditory apperceptive agnosia may be divisible into a number of distinct disorders. For example, reports of individual patients with apperceptive auditory agnosia are heterogeneous, with considerable variation in the categories of sounds that are affected; single case reports have described the selective impairment of words, environmental sounds and music (e.g. Fujii et al., 1990; Habib et al., 1995; Griffiths et al., 1997; Wang et al., 2000; Saygin et al., 2010). As already suggested, the detailed psychoacoustic interrogation of underlying deficits in such cases tends to reveal particular profiles of fine-grained perceptual property deficits which may affect spectral, temporal and/or spectrotemporal processing; however, since deficits cause most impairment at the object processing level, it is argued that these patients suffer apperceptive rather than property processing disorders. Furthermore, since auditory categories tend to exhibit stereotypical acoustic characteristics (Singh and Theunissen, 2003), it can be suggested that impairments biased towards words, environmental sounds or music may emerge because certain fine-grained property deficit profiles hold particular relevance to the disrupted category; as will be described below, the empirical

evidence supports this assertion. Thus, neuropsychological reports of apperceptive agnosia suggest a heterogeneous range of fine-grained spectrotemporal disorders that particularly impair object processing within circumscribed object categories (Griffiths et al., 1999). Together, this evidence suggests that object apperception in the healthy brain may reflect a broad stage of cognition that is divisible into multiple sub-processes.

1.5.3.3 The fine-grained spectrotemporal basis of apperceptive deficits: word deafness

There is a small literature detailing auditory impairments that are relatively selective for the category of words, i.e., word deafness. However, the term word deafness has been applied inconsistently, referring to disorders that reflect distinct underlying cognitive impairments. For example, limited evidence indicates both phonological and semantic subtypes of this syndrome (Saffran et al., 1976; Caramazza et al., 1983; Metz-Lutz and Dahl, 1984; Kohn & Friedman, 1986; Praamstra et al., 1991; Franklin et al., 1996; Plasenciaet al., 2005); however, patients with word deafness caused by perceptual impairments hold most relevance to the present discussion. The majority of perceptual word deafness cases can be attributed to predominant property processing impairments, specifically involving reduced auditory temporal resolution (see section 1.5.2.2.1), and such deficits may occur either following stroke (e.g., Albert and Bear, 1974; Auerbach et al., 1982; Miceli, 1982; Tanaka et al., 1987; Yaqub et al., 1988; Buchtel and Stewart, 1989), or in the context of primary progressive aphasia (e.g., Otsuki et al., 1998). These patients are often unable to distinguish simple sounds presented in quick succession (e.g., pairs of noise bursts), and instead perceptually ‘fuse’ multiple stimuli into a single object (e.g., Albert and Bear, 1974; Auerbach et al., 1982). Additionally, these cases typically lead to secondary deficits not only for the apperception of words, but for multiple categories of sound objects, indicating a broad property processing disorder that is unlikely to fit the definition of auditory apperceptive agnosia offered above (section 1.6.3.1). However, further reports of word deafness describe qualitatively different cases involving fine-grained property processing deficits that cause disproportionately severe and relatively category-specific impairments for words (Wang et al., 2000; Stefanatos et al., 2005); according to

the above definition, such deficits may be considered auditory apperceptive agnosia. Indeed, auditory apperceptive agnosia for words might be predicted a priori, given that this object category shows a high degree of acoustic homogeneity and would therefore exhibit particular vulnerability to circumscribed property processing disorders within relevant spectrotemporal parameter ranges. Specifically, words tend to feature a complex mixture of harmonic sounds, broad-band noise and silent gaps, joined by accurately timed transitions occurring at the scale of milliseconds (Griffiths et al., 1999). Whilst environmental sounds and melodies contain similar components, they do not feature similarly precise or rapid transitions; therefore, the apperception of words as opposed to other sound objects would be selectively impaired by fine-grained deficits of rapid spectrotemporal processing. Indeed, the psychoacoustic interrogation of a subset of word deafness patients has revealed circumscribed spectrotemporal deficits underlying more prominent apperceptive impairments (Wang et al., 2000; Stefanatos et al., 2005). For example, Wang et al. (2000) describe a word deaf patient who, following a stroke, could not discriminate between consonant-vowel-consonant pairs such as ‘pet’ and ‘pat’, but could discriminate their constituent vowels when presented in isolation. Additionally, the patient was unable to discriminate the direction of upward and downward pure tone frequency sweeps. These findings suggests that in this case, deficits for word perception were caused by circumscribed impairments for discriminating temporally rapid transitions between spectral sounds, i.e., spectrotemporal information. Similar deficits were evident in the stroke patient of Stefanatos et al., (2005), who furthermore retained the ability to recognize other categories of auditory objects such as environmental sounds. Thus, a small subset of word deafness cases exemplify the syndrome of apperceptive auditory agnosia according to the above definition, i.e., deficits that causes relatively greater impairments at the object than the property processing level, which furthermore, exhibit relative category-specificity. However, the prevalence of word deafness involving predominant perceptual property deficits, together with evidence for an influence of property processing impairments upon apperceptive cases, suggests that auditory apperception shows only limited cognitive independence, and is likely to be reliant upon input from related stages of processing.

1.5.3.4 The fine-grained spectrotemporal basis of apperceptive deficits: non-verbal sounds

Apperceptive impairments that are relatively selective for environmental or other non-verbal sounds have been documented with less frequency than those that affect the perception of words. This may be due, at least in part, to the increased saliency of verbal deficits which are more likely to impair activities of daily living. However, the rarity of non-verbal apperceptive deficits might also reflect the relatively greater acoustic heterogeneity of environmental sounds in comparison to words, which vary widely in spectral, temporal and spectrotemporal structure. For example, some environmental sounds predominantly consist of noise with relatively slow modulations (e.g., sounds made by hand tools), whilst others are formed from harmonic complexes with rapid changes (e.g., animal calls). Thus, if fine-grained spectrotemporal processing impairments form the basis of apperceptive agnosia, such deficits might not affect non-verbal sounds in general, but specific subsets of sounds that share spectrotemporal characteristics. This prediction is supported by a recent report describing a stroke patient with auditory agnosia but without word deafness (Saygin et al., 2010); here, evidence was provided for an association between environmental sound recognition and spectrotemporal structure, such that sounds with structures dissimilar to words were less likely to be recognized. This finding suggests that fine-grained spectrotemporal impairments may lead to predominant apperceptive disorders for non-verbal sounds; moreover, it also indicates that the specific spectrotemporal impairments involved are likely to be qualitatively different to those associated with word deafness, perhaps affecting the analysis of relatively slower modulations. These suggestions gain further support from additional cases involving the selective impairment of other non-verbal sound categories. For example, Peretz and colleagues (1994) reported two stroke patients who showed simultaneous deficits for the discrimination of melodies and prosody, i.e., sound sequences that feature perceptually important slow modulations, despite preserved word and environmental sound perception. In a further case, Griffiths et al. (1997) provided direct evidence that selective deficits of melody discrimination following stroke may reflect specific impairments for temporal processing within relatively long time-frames. Additionally, since voices are a homogenous sound category in which identity is indicated by subtle differences of spectral structure, selective deficits of voice

discrimination (‘apperceptive phonagnosia’) may be caused by circumscribed deficits for detailed spectral analysis (Van Lancker and Kreiman, 1987; Van Lancker et al., 1988; Van Lancker et al., 1989; Peretz et al., 1994; Neuner and Schweinberger, 2000). To summarize, evidence supports the existence of apperceptive agnosia for non-verbal sounds according to the definition given above, and suggests that the syndrome is likely to involve fine-grained spectrotemporal deficits that are qualitatively different from those found in word deafness, affecting the analysis of slow modulations and/or rich spectral detail. Further, differences in the specific sound categories affected (e.g., environmental sounds, melodies, voices) may reflect subtle variations in the spectrotemporal range of deficits. Again, the influence of property processing impairments upon apperceptive non-verbal deficits, alongside the rarity with which such disorders are reported, suggests that auditory apperception shows only limited cognitive independence, and is likely to be reliant upon input from related stages of processing. However, cases of auditory apperceptive agnosia taken together indicate that the syndrome may be divisible into a number of heterogeneous disorders that particularly affect certain object categories; thus, auditory object apperception may involve multiple distinct sub-processes.

1.5.3.5 Auditory apperceptive deficits: anatomical evidence

The anatomical picture of auditory apperceptive agnosia is complex (for comprehensive meta-analyses see Griffiths et al, 1999, Simons and Lambon Ralph, 1999). However, responsible lesions tend to involve primary and/or association auditory cortices bilaterally, and their connections (Griffiths et al., 1999), and there is considerable anatomical overlap between apperceptive agnosias affecting distinct sound categories. Several reports diverge from this pattern, showing sparing on one or both sides of primary and/or association auditory cortex; however, reports do not rule out the possibility that ‘spared’ regions could be functionally (rather than structurally) damaged as a result of underlying white matter damage (Griffiths et al., 1999). Whilst the anatomical overlap between apperceptive agnosias for distinct categories might suggest the presence of shared cortical mechanisms, a degree of independence is also suggested by limited evidence for category-specific substrates. For example, apperceptive cases of word deafness have been associated with unilateral left-

sided damage to the auditory association cortex (superior temporal gyrus; Wang et al., 2000; Stefanatos et al., 2005). In contrast, apperceptive deficits for processing non-verbal sounds have been associated with right-sided temporal damage (Fujii et al., 1990; Eustache et al., 1990; Schnider et al., 1994; Griffiths et al., 1997; Vignolo, 2003), although conflicting evidence also exists (Van Lancker and Kreiman, 1987; Van Lancker et al., 1989; Habib et al., 1995; Saygin et al., 2010). A lack of consistent and rigorous testing makes it difficult to delineate the source of variability in the available anatomical data. However, the evidence collectively suggests that damage to different regions of the left and right auditory cortices may lead to apperceptive disorders that are particularly relevant to different sound object categories.

1.5.3.6 Studies of auditory apperceptive processing in healthy subjects

1.5.3.6.1 Object-specific combinations of property representations in auditory cortices provide key inputs for apperceptive processing

As already described (see section 1.5.2.2.2), healthy subjects show specialization throughout different regions of right and left auditory cortices for the processing of different spectral and temporal properties (Giraud et al., 2000; Zatorre and Belin, 2001; Poeppel, 2003; Boemio et al., 2005; Schönwiesner et al., 2005; Altmann et al., 2010). Further, spectral and temporal representations may be integrated in posterior regions of auditory association cortex, such as PT, to generate spectrotemporal property representations (Altmann et al., 2010). This evidence suggests that object-specific property combinations may elicit object-specific profiles of auditory cortical activity, which provide key inputs for subsequent apperceptive processes. Thus, the topographical organisation of perceptual properties in the healthy brain may provide an anatomical basis for the heterogeneous range of category-specific auditory apperceptive agnosias reported in the neuropsychological literature. Whilst relatively gross damage to the auditory cortices might lead to rather broad perceptual property processing deficits (e.g., dystimbria, see section 1.5.2.2.1), more circumscribed damage to sub-regions might selectively disable the key inputs required for the apperception of particular sound categories, by virtue of their typical spectral,

temporal, or spectrotemporal structures. For example, damage to circumscribed regions of auditory cortex associated with shorter and longer ‘time-windows’ of temporal property processing might lead to apperceptive agnosias that particularly affect words and environmental sounds respectively. Alternatively, damage to regions specifically involved in processing fine-grained spectral detail may result in apperceptive phonagnosia.

1.5.3.6.2 Initial apperceptive representations in the planum temporale

Additional studies of human subjects suggest that property representations may be combined to form initial apperceptive representations during a discrete cognitive process involving ‘auditory template’ processing in the PT. As already outlined (section 1.5.3.1), the brain may contain a library of stored auditory templates which specify the typical spectrotemporal characteristics of familiar sound objects in a relatively abstract code. In particular, one influential model suggests that object representations may be generated via a process that matches incoming sound mixtures to auditory templates (Griffiths and Warren, 2002). Further, it is held that auditory templates contain information about the non-linear relations between properties and objects (as a result of previous auditory experience), which would specifically facilitate auditory apperceptive processing despite varying listening conditions, i.e., auditory object invariance (Griffiths and Warren, 2002). However, it is likely that the apperceptive representations generated by this matching algorithm are preliminary, and require subsequent processing in other regions of auditory association cortex for full elaboration of spectrotemporal detail and sound identification. Although the specific details of the computations involved in auditory template processing have yet to be worked out (Griffiths and Warren, 2002; Warren et al., 2005b), a range of empirical data suggests a candidate anatomical substrate in the planum temporale (PT), which is situated in posterior auditory association cortices (Griffiths and Warren, 2002). For example, a substantial literature of imaging studies involving healthy subjects show that the PT responds strongly to any sound with a complex spectrotemporal structure (Griffith and Warren, 2002; Warren et al., 2005b). Additionally, studies that directly assess the segregation of sound mixtures into individual objects suggest a key role for the

PT (Deike et al., 2004; Wilson et al., 2007; Gutschalk et al., 2007; Deike et al., 2010; Overath et al., 2010; Smith et al., 2010; Schadwinkel and Gutschalk, 2010). Furthermore, the PT is preferentially activated irrespective of the specific spectrotemporal cues involved in scene segregation (Deike et al., 2004; Deike et al., 2010; Smith et al., 2010), and may therefore constitute a general-purpose computational engine that performs the first stages of apperception for all types of complex sound objects (Warren and Griffiths, 2002). Additionally, direct evidence for auditory object invariance, and thus the action of auditory object templates, has been provided by electrophysiological investigations of cat auditory cortex (Nelken and Bar-Yosef, 2008). Here, studies have described responses in single neurons of primary auditory cortex to particular auditory object stimuli (e.g. a particular pattern of background noise), that remain constant despite variation in simultaneously present sound objects (e.g., bird calls; Bar-Yosef and Nelken, 2007). Thus, the primary auditory cortex might form auditory templates of background noise which are invariant to changes in the overall sound mixture. Whilst the investigators did not examine non-primary auditory cortices, it is plausible that these would process similar or more complex auditory object templates. Taken together, the human and animal literatures suggest that the initial stages of auditory apperceptive processing are based upon the application of stored auditory templates within the PT; thus, damage to this region might in principle lead to category-general apperceptive deficits, although this hypothesis awaits substantiation with neuropsychological data.

1.5.3.6.3 Elaborated auditory object representations in antero-ventral auditory association cortices

Further fMRI studies in healthy subjects suggest that the outputs of initial apperceptive processes in posterior auditory cortices and the planum temporale are subsequently passed onto more anterior and ventral regions of auditory association cortices, where they are represented in more detail. For example, a range of studies suggest that particular circumscribed areas of the temporal lobe, situated anterior and ventral to the primary auditory cortex in the superior temporal gyrus and sulcus, selectively respond to particular sound categories, such as words, voices or musical instruments (Scott et al., 2000; Belin et al.,

2000; Belin et al., 2002; Belin and Zatorre, 2003; Warren et al., 2006; Leaver and Rauschecker, 2010); such category-specific organisation suggests the presence of fully elaborated apperceptive representations that could ultimately be used to guide behaviour. More recent studies, however, have provided additional insight into the functional organisation of this region. For example, Leaver and Rauschecker (2010) isolated activity relating to the auditory apperceptive representation of a range of sound categories by co-varying for a range of basic auditory properties. Some categories elicited anatomically circumscribed responses in anterior-ventral auditory association cortex (musical instruments in right anterior superior temporal plane, words in left mid superior temporal sulcus); however, others (animal calls, bird song) did not, suggesting that they may depend upon more distributed representations (Leaver and Rauschecker, 2010). Further evidence for the presence of distributed in addition to circumscribed apperceptive representations within these regions has been provided by a second study (Staeren et al., 2009); here, three categories (guitars, females singers, cats), equalised for basic perceptual properties, elicited differential patterns of activity throughout similar regions of primary, secondary and association auditory cortex. Thus, the anterior-ventral auditory association cortices appear to contain regions for both category-specific and category-general object representation.

Further examination of category-specific responses within anterior-ventral auditory association cortices suggests that they may be driven, to some extent, by regional specialisation for the processing of particular category-relevant spectrotemporal properties. The category of voices is a particularly good test case of this hypothesis: since voices are relatively perceptually homogeneous, voice discrimination depends upon the detection of subtle discrepancies in spectral shape. Thus, Lewis and colleagues (2009) scanned subjects whilst they listened to either voices or analogous artificial stimuli with varying levels of Harmonic-to-Noise ratio (HNR), an index of spectral complexity (Lewis et al., 2009). Results showed that increases in HNR correlated with activity in cortices located between posterior property perception and anterior voice-selective regions. Thus, category-specific responses within anterior-ventral auditory association cortices may be at least partially dependent upon regional specialisation for particular spectrotemporal properties. Further, this evidence

would suggest that any perceptually homogeneous category might elicit anatomically circumscribed responses; however, as already described, other studies failed to find circumscribed regions corresponding to the perceptually homogeneous categories of guitars, animal calls and bird song (Staeren et al., 2009; Leaver and Rauschecker, 2010). Such observations may indicate that the functional organisation of anterior-ventral auditory regions depends not only upon spectrotemporal properties, but also upon category-specific factors such as familiarity, behavioural relevance, or evolutionary significance. These suggestions might also explain why Lewis and colleagues (2009) found correlates of HNR near to, but not within, voice-selective regions. A combination of spectrotemporal and category-specific organizational factors would conceivably drive regional specialisation for categories that are both spectrotemporally homogeneous and behaviourally important; this contention is supported by the neuroimaging evidence for relatively circumscribed regions corresponding to both words and voices (Scott et al., 2000; Belin et al., 2000; Belin et al., 2002; Belin and Zatorre, 2003; Warren et al., 2006; Leaver and Rauschecker, 2010). Further, given that specialised regions would combine spectrotemporal and category-specific information, possibly in a non-linear fashion, corresponding apperceptive representations are likely to show a degree of independence from spectrotemporal structure. Thus, damage to regions that are specialized for processing voices or words might lead to corresponding category-specific apperceptive agnosias with relatively few accompanying property processing deficits. In contrast, more widespread damage might lead to category-general apperceptive deficits, although, as already noted, the literature does not contain any such cases.

1.5.3.6.4 Studies of auditory apperceptive processing in healthy subjects: section summary

Taken together, neuroimaging studies of healthy controls are consistent with a hierarchically organized auditory apperceptive processing network: initially, basic auditory properties are encoded and combined into preliminary object representations within posterior-dorsal regions and particularly the planum temporale; subsequently these representations are progressively elaborated along an anterior-ventral pathway. Many regions of this network show

specialisation for particular spectrotemporal properties, which may hold particular relevance to certain sound categories. However, as representations progress towards anterior-ventral areas, there is increasing regional specialisation for particular sound categories such as words and voices, indicating the presence of detailed apperceptive representations that might ultimately guide behaviour. Such observations are consistent with evidence from neurophysiological studies of animals, which reveal that neurons along an antero-ventral temporal pathway show increasing specialisation for acoustically complex and behaviourally relevant sound objects, such as species-specific vocalisations (Rauschecker, 1998; Kaas and Hackett, 1999; Romanski et al., 1999). Taken together, the literature may suggest that auditory apperception depends upon a distributed processing network traversing superior posterior and anterior-ventral temporal regions; however, circumscribed regions of this network are likely to show functional specialisation for particular sub-processes such as template processing or category-specific representation.

1.5.3.7 Auditory apperceptive processing: section summary

The term apperceptive processing refers to mechanisms that enable the perceptual representation of whole objects, prior to the attribution of meaning. Research in the visual modality indicates an independent stage of apperceptive processing; however, it remains unclear whether analogous mechanisms are similarly pervasive in the auditory modality. Here, auditory apperceptive agnosia is operationally defined as an auditory object processing deficit that is disproportionately severe in comparison to any accompanying impairments of property processing. A review of available single case reports suggests that auditory apperceptive agnosia may consist of a spectrum of heterogeneous fine-grained property analysis impairments that disproportionately affect the perceptual representation of certain sound object categories, by virtue of their typical spectrotemporal structures (e.g., words, environmental sounds, voices, music); further, there are tentative correlations between the affected sound category and lesion location. Thus, the neuropsychological literature, whilst limited, provides some evidence for a relatively independent stage of auditory apperception; however, data also suggest that auditory apperception shows partial dependencies upon other processes, in particular property perception.

Neuroimaging studies of healthy subjects provide a broad anatomical basis for this neuropsychological data. Firstly, there is topographical organization of spectral, temporal, and spectrotemporal property representations within posterior-dorsal regions of auditory cortices, such that circumscribed damage might selectively disable key inputs for the apperception of certain sound categories with corresponding perceptual structures. Secondly, the planum temporale may be a general-purpose computational engine that performs the initial stages of apperception for all types of sound object; thus, damage to this region might lead to category-general auditory associative agnosia. Lastly, anterior-ventral regions of auditory cortices may contain fully elaborated apperceptive representations of auditory objects, which would ultimately be used to guide behaviour. Within this region, representations of behaviourally important categories are regionally circumscribed (e.g., words, voices), whilst representations of other sounds are distributed (e.g., cats, guitars); thus, topographical organization here may be driven by both spectrotemporal and category-specific factors, and circumscribed damage might lead to category-specific apperceptive deficits accompanied by relatively few perceptual property processing impairments. Taken together, the literature may suggest that auditory apperception depends upon a distributed processing network centred upon the temporal lobes, including various regions that show functional specialisation for particular sub-processes.

1.5.3.8 Auditory apperceptive processing deficits in dementia

Whilst relevant investigations in dementia are sparse, a small body of literature provides evidence for category-specific auditory object processing deficits (words in AD: Eustache et al., 1995; environmental sounds in AD: Rapcsak et al., 1989, Eustache et al., 1995; prosody in AD: Testa et al., 2001; words in PPA: Otsuki et al., 1998, Jorgens et al., 2008, Iizuka et al., 2007; environmental sounds in PPA: Uttner et al., 2006; prosody in PPA: Confavreux et al., 1992, Yamamoto et al., 2004). In particular, a number of studies describe progressive word deafness or agnosia for nonverbal sounds as leading features in patients with PNFA-like syndromes, many in the Japanese literature (Confavreux et al., 1992; Otsuki et al., 1998; Kuramoto et al., 2002; Kaga et al., 2004; Yamamoto et al., 2004; Uttner et al., 2006; Iizuka et al., 2007; Jorgens et al., 2008). In most

cases, the cognitive locus of impairment is not adequately indicated, and thus it is unclear whether patients suffer apperceptive or associative agnosias. However, in at least one report, psychoacoustic investigation provided evidence for a fine-grained spectrotemporal deficit, thus suggesting the presence of an apperceptive disorder (Otsuki et al., 1998). Additionally, the topography of cortical damage in various dementia syndromes indicates the possibility of apperceptive disorders. For example, since damage in PNFA, AD and LPA encompasses posterior-dorsal auditory cortices, patients might show auditory property processing deficits that lead to predominant impairments of object apperception for certain categories of sound. Additionally, AD (and to a lesser extent PNFA and LPA) involves prominent atrophy in posterior temporo-parietal regions; such damage might disable mechanisms in the PT for the initial apperception of auditory objects, leading to category-general auditory apperceptive agnosia. Finally, SD, PNFA, AD and LPA involve various topographies of atrophy throughout anterior-ventral auditory cortices, which might lead to disorders for processing detailed apperceptive representations. Further, if damage is focused upon particular sub-regions, such deficits may emerge with category-specificity. Thus, present investigations will assess apperceptive processing in a range of dementia syndromes with atrophy to implicated cortices (SD, PNFA, LPA, AD); comparisons of behavioural deficits and anatomical damage between syndromes may help to illuminate the cortical organization of corresponding functional networks.

1.5.4 Auditory scene analysis deficits

1.5.4.1 An introduction to auditory scene analysis

Up until now, this review has been concerned with the processing of individual auditory properties or objects. However, in everyday life, humans are generally surrounded by multiple, overlapping sounds generated by a range of sources in the environment. To make sense of these complex scenes, the brain must determine which acoustic properties belong to which sound sources, or in cognitive terms, parse the auditory scene into constituent sound objects. Thus, auditory processing involves mechanisms by which object properties are separated from the acoustic background (object segregation) and bound

together as discrete perceptual entities (object representation). These cognitive operations are collectively termed ‘auditory scene analysis’ (ASA, Bregman, 1990), although they overlap considerably with processes of object apperception (see section 1.5.3). In general, evidence suggest that ASA is mediated by both ‘bottom-up’ and ‘top-down’ auditory perceptual mechanisms, and is additionally supported by a range of executive (e.g., attentional) processes (Bregman, 1990; Alain and Arnott, 2000; Snyder and Alain, 2007; Winkler et al., 2009).

Bottom-up mechanisms involve the parsing of auditory scenes according to simple acoustic properties such as frequency and amplitude (Bregman, 1990; for a review, see Fishman and Steinschneider, 2010). For example, properties that are harmonically related, or that begin and end together in time, are likely to emerge from the same object and are therefore grouped together; in contrast, properties that arise from different spatial locations, or that are widely spaced in frequency or time, tend to come from different objects and are correspondingly segregated (Fishman and Steinschneider, 2010).

Top-down mechanisms involve the parsing of scenes according to prior auditory perceptual knowledge. Here, prior knowledge is held to involve stored ‘auditory templates’, i.e., relatively abstract perceptual representations of sound objects (Griffiths and Warren, 2002; see section 1.5.3.1). From this perspective, ASA proceeds via the matching of incoming sound mixtures to stored auditory templates; such a process would therefore bias processing towards the formation of certain previously encountered objects. Although, behavioural investigations of auditory template processing during ASA are lacking, indirect evidence suggests their utility in the perception of natural scenes (e.g. Leech et al., 2009).

The combined action of bottom-up, top-down and executive mechanisms during ASA has been demonstrated through the use of ‘dual-stream’ paradigms, in which two sequences of tones (one at a lower pitch and faster rate than the other) are superimposed to create a percept of either one combined stream or two separate streams (Bregman, 1990; for auditory examples see Carlyon et al., 2003). Here, perceptual segregation into two streams can be promoted by

either bottom-up processing (e.g., if tones are further apart in frequency), top-down processing (e.g., via stored perceptual knowledge, i.e. auditory templates, of the segregated percepts), and/or executive processing (e.g., attentional shifts following changes to task instructions; Bregman, 1990; Moore and Gockel, 2002, Snyder and Alain, 2007). Thus, auditory scene parsing solutions vary according to a range of cognitive factors. Furthermore, the relative influence of different bottom-up, top-down and executive sub-processes is likely to vary in a context-dependent manner to produce behaviourally relevant ASA solutions (Cusack et al., 2004); such flexibility is useful in the natural environment which frequently contains scenes with multiple objects and parsing solutions.

1.5.4.2 ASA: neuropsychological studies

Very few studies have conducted specific investigations of ASA in neurological patient populations. Cusack and colleagues (2000) studied patients with the syndrome of unilateral neglect (UN) and right-sided damage to the intra-parietal sulcus. UN involves a lack of awareness for objects on the contra-lesional side of space and is therefore primarily considered a spatial attention disorder (e.g., Barrett et al. 2010); however, further evidence shows that the syndrome may also affect auditory attention (Carlyon et al., 2001). In support of this notion, Cusack et al. (2000) showed that UN patients were worse at comparing auditory features between multiple objects than within single objects, and that this deficit was not related to spatial factors. This study therefore suggests that attending to and organising multiple objects within a scene, in association with the intra-parietal sulcus, may constitute a relatively independent executive sub-process of ASA.

1.5.4.3 ASA in healthy human subjects and animals

1.5.4.3.1 General ASA processes in healthy human subjects and animals

A growing literature of functional imaging studies in healthy populations has provided more insight into the brain systems that govern ASA. A large body of electroencephalography (EEG) studies have used event-related potentials (ERPs) as markers to delineate temporally successive stages of ASA (for a

review, see Snyder and Alain, 2007). However, this methodology lacks spatial resolution, and investigations using fMRI have provided more detailed information about the network of brain substrates involved in ASA. For example, using the 'dual stream' paradigm (see above), a number of fMRI studies have shown that activity levels in both primary and non-primary auditory processing regions, including the planum temporale (PT), corresponds to the perception of one or two streams (Deike et al., 2004; Wilson et al., 2007; Gutschalk et al., 2007; Schadwinkel and Gutschalk, 2010; Deike et al., 2010). In particular, Wilson et al. (2007) have demonstrated that activity in both primary and association auditory cortex correlates with the tendency to perceive two streams rather than one, i.e., stream segregation. Additionally, further studies have suggested the involvement of parietal and frontal regions associated with various executive (attentional) processes that may support ASA (e.g., Cusack et al., 2005; Schönwiesner et al., 2007).

1.5.4.3.2 Bottom-up and top-down ASA processes in healthy human subjects and animals

A range of empirical evidence supports the dissociation of bottom-up and top-down sub-processes of ASA. Firstly, bottom-up mechanisms, involving the parsing of scenes according to simple auditory properties, have been revealed by investigations of 'dual stream' segregation based upon frequency cues. Using this paradigm, intra-cellular recordings in animals have located cortical mechanisms for bottom-up ASA in regions homologous to human primary auditory cortex. Further, results suggest that such mechanisms rely upon both the frequency selectivity of neurons in tonotopically organised primary auditory cortex, and a process of inter-neuronal suppression (also known as 'forward masking'; Fishman et al., 2001; Fishman et al., 2004; Fishman and Steinschneider, 2010). Here, when two superimposed streams are close in frequency, corresponding neural representations are spatially proximate in tonotopic auditory cortex and suppress one another; since neither stream dominates, a single stream is perceived. In contrast, when the frequency separation of superimposed streams is greater, there is more spatial differentiation and less suppression between corresponding neural representations, and two segregated streams are perceived. Thus, by

describing neural mechanisms located in primary auditory regions which operate on the basis of simple perceptual cues, these data provide evidence for bottom-up ASA processes.

Complementary studies using fMRI in healthy human populations suggest the presence of relatively independent bottom-up and top-down ASA mechanisms. In particular, one pair of fMRI studies (Deike et al., 2004; Deike et al., 2010) compared dual-stream segregation driven by a simple perceptual property (pitch) and a more complex spectrotemporal one (timbre). Results showed that segregation based upon pitch but not timbre led to activity increases in primary auditory cortex (Deike et al., 2010), indicating the presence of bottom-up ASA processes when simple perceptual cues were available. However, segregation based upon either pitch or timbre led to activity increases in posterior regions of auditory association cortices including the PT (Deike et al., 2004; Deike et al., 2010). In a further investigation, Smith et al. (2010) used fMRI to scan subjects whilst they listened to auditory stimuli containing variations in two perceptual properties likely to be associated with distinct cortical representational processes. Specifically, stimuli were mixtures of speech sounds containing varying numbers of speakers (an object property) at varying locations (a spatial property). Results showed selective activity in the PT which increased with either the number of speakers or the number of locations. Thus, although all three studies described here (Deike et al., 2004; Deike et al., 2010; Smith et al., 2010) investigated ASA driven by different perceptual cues (simple perceptual properties (pitch), complex perceptual properties (timbre), spatial information (spatial location), and complex object representations (voices)), each revealed correlated activity in the PT. It can therefore be suggested that the function of PT is not limited to simple perceptual property encoding or bottom-up ASA mechanisms. In particular, since the PT is implicated irrespective of the type of auditory percept involved, it is likely to perform ASA computations based upon a process of matching incoming information to stored perceptual knowledge, i.e., the top-down application of auditory templates. Notably, such conclusions are supported by a range of previous work (Griffiths and Warren, 2002). Additionally, the pair of studies by Deike and colleagues provides evidence for a relative anatomical dissociation between top-down and bottom-up ASA

processes, which are predominantly associated with association and primary auditory cortices respectively (Deike et al., 2004; Deike et al., 2010).

Finally, further fMRI studies involving healthy human subjects have sought to describe ASA processes of object segregation and object representation in terms of underlying bottom-up and top-down mechanisms. For example, Overath et al. (2010) scanned subjects whilst listening to varying sequences of synthetic auditory “textures”: here, object segregation was indexed by perceptual differences between consecutive textures, and object representation was indexed by salient texture characteristics. Results suggested that object segregation was associated with activity in primary and association cortices, whilst object representation was associated with activity in auditory association cortices only. Very similar anatomical associations are provided by one further study involving combined fMRI-EEG and an auditory ‘oddball detection’ paradigm (Schönwiesner et al., 2007); additionally, this study provided evidence for a temporal dissociation between the ASA processes involved, specifically suggesting that object segregation precedes object representation. Taken together, these findings suggest that object segregation is an earlier process that depends on a combination of bottom-up and top-down mechanisms throughout primary and association auditory cortices, whilst object representation is a later process that depends upon top-down processes in association auditory cortices including PT.

1.5.4.3.3 Executive ASA processes in healthy subjects

Further studies highlight the importance of executive processes in ASA. Whilst a range of overlapping cognitive functions including attention, monitoring, working memory and cognitive control are likely to be relevant, most research has focussed upon the role of attention (Snyder and Alain, 2007). Here, evidence demonstrates a range of attentional processes that support ASA, associated with varying cortical regions. For example, research suggests the presence of an independent mechanism for attending to segregated objects within a scene, which is both temporally and spatially dissociated from the auditory perceptual processes that facilitate initial scene segregation (Schönwiesner et al., 2007). Specifically, Schönwiesner and colleagues used

fMRI-EEG and an ‘oddball’ detection task to show that prefrontal activity associated with attending to an object occurred subsequently to activity in the auditory cortices associated with scene segregation. Additionally, a distinct attentional ASA mechanism has been described in a pair of studies by Cusack and colleagues (Cusack et al., 2000; Cusack, 2005). Using fMRI to scan healthy controls during a ‘dual stream’ task, greater activity was found in the intra-parietal sulcus (IPS) when two streams were perceived compared to one (Cusack et al., 2005). The interpretation of this data was assisted by an earlier study (described above; Cusack et al., 2000), showing that patients with IPS damage are impaired in attending to multiple compared to single auditory objects. Taken together, this pair of studies suggests the presence of a discrete attentional process located in the IPS which enables attending to multiple auditory objects in a scene. Many further studies have described other attentional processes relevant to ASA (e.g., Alain and Arnott, 2000; Snyder and Alain, 2007), although the predominant use of EEG methodology limits the anatomical conclusions that may be drawn. Taken together, the range of evidence suggests the presence of several heterogeneous and relatively independent attentional processes that support ASA in association with various cortical regions. Additionally, further work suggests that these processes operate in a highly context-dependent manner (e.g., Cusack et al., 2004; see also Bregman, 1990). However, whilst results vary, many studies describe attentional processes that impact less upon the initial parsing of auditory scenes and more upon the selection of pre-segregated objects, thus emphasising a dissociation between perceptual and executive processes during ASA (Alain and Arnott, 2000; Cusack et al., 2005; Schönwiesner et al., 2007).

1.5.4.4 ASA: section summary

The studies reviewed above suggest that ASA may involve a number of independent bottom-up, top-down and executive mechanisms that occur throughout a network of closely associated brain regions. Bottom-up mechanisms comprise processes of object segregation based upon simple perceptual properties in primary auditory cortex. Top-down mechanisms comprise processes of object segregation based upon the application of auditory templates in association cortices including PT. Additionally, object

segregation is likely to involve a combination of bottom-up and top-down mechanisms, whilst the representation of segregated objects is likely to rely more heavily upon top-down processing. Furthermore, a variety of executive (and particularly attentional) mechanisms involving regions extrinsic to the auditory cortices, such as the intra-parietal sulcus and prefrontal cortex, are likely to support perceptual ASA mechanisms; for example, such processes may facilitate attending to individual or multiple segregated objects within a scene. Finally, limited neuropsychological evidence suggests that patients may suffer selective deficits affecting discrete sub-processes of ASA, thus indicating relatively independent stages of cognitive processing.

1.5.4.5 ASA in dementia

The distribution of ASA processes in the healthy brain suggests that ASA deficits may occur in dementia syndromes involving atrophy to posterior temporal and inferior parietal regions including the PT, such as PNFA, LPA and AD. However, behavioural and neuroimaging evidence particularly suggests that ASA deficits may occur relatively commonly and early in the course of Alzheimer's disease (AD; see section 1.6.5). At presentation, patients with AD commonly complain of difficulty in tracking auditory information streams, for example, when following conversations in the presence of background noise. In both early and pre-symptomatic AD groups, subjects show impairments on verbal tasks that are likely to depend upon ASA processes (e.g., 'sentence competition' tasks requiring attention to one of two simultaneously presented sentences; Gates et al,. 1996; Gates et al,. 2002; Gates et al., 2008), and altered cortical function during auditory 'oddball' detection and other auditory processes relevant to ASA (Golob et al., 2007; Golob et al., 2009). This evidence indicates that AD may lead to prominent ASA impairments affecting verbal and non-verbal stimuli alike.

1.5.5 Semantic processing deficits

1.5.5.1 Theoretical models of semantic processing

The term semantic processing refers to the association of perceptual object representations with stored conceptual knowledge, and there is a rich literature concerning corresponding neuropsychological deficits. Perhaps as a result, semantic processing has been theoretically conceptualised in a number of different and apparently conflicting ways. Therefore, before embarking upon a description of the neuropsychological literature of auditory semantic processing deficits, it is useful to consider briefly the various theories that have been proposed.

Although the details vary, all theories suggest a mechanism by which links between representations of object features are coded to produce a unified conceptual object representation that is stored in semantic memory. However, there are significant variations in the degree to which theories incorporate two broad types of semantic representations; these will be referred to in what follows by the terms ‘multi-modal’ and ‘amodal’. Multi-modal semantic representations involve, to some extent, information that is coded directly within one or more modalities, i.e., modality-specific information (Warrington and McCarthy, 1983; Warrington and Shallice, 1984; Warrington and McCarthy, 1987; Damasio, 1989; Tranel et al., 1997; Caramazza and Shelton, 1998; Crutch and Warrington, 2003; Barsalou et al., 2003; Pulvermüller, 2005). For example, a multi-modal semantic representation of an elephant call would involve information coded in auditory form. However, multi-modal representations in one modality cannot interact directly with those in another modality. In contrast, amodal representations are held to code semantic information in abstract form, typically as patterns of statistical correlations between object features (Devlin et al., 1998; Tyler and Moss, 2001; Rogers and McClelland, 2004). It is suggested that amodal representations are essential to the semantic system because they provide means to integrate semantic knowledge across different modalities, for example, to derive a unified concept of an elephant, including visual, auditory, tactile, and chemosensory information. Additionally, amodal representations may also provide the means to generalise semantic knowledge to novel or atypical objects, thus facilitating tasks such as the recognition of unusual tools or animals (Lambon Ralph et al., 2010; Mayberry et al., 2010).

The range of semantic processing theories and their inter-relationships have been recently articulated by Crutch and Warrington (submitted) as follows. Firstly, 'distributed-only' models suggest that links between object features are coded in multi-modal form, i.e., by associations between perceptual representations (e.g., Glenberg and Kaschak, 2002; Barsalou et al., 2003; Pulvermüller, 2005). Secondly, 'distributed-plus-convergence' models envisage similar multi-modal links, plus the action of convergence zones (CZs) in which common combinations (conjunctions) of object features are represented in predominantly amodal form (e.g., Damasio, 1989; Tranel et al., 1997; Murray and Bussey, 1999; Bussey and Saksida, 2002; Tyler et al., 2004; Martin, 2007). In this framework, theorists envisage a hierarchical organisation of increasingly complex CZs which, at more basic levels code conjunctions between particular features within modalities (e.g., in animals, the co-occurrence of particular face and body shapes), and at more complex levels code conjunctions between two or more modalities (e.g., in animals, the co-occurrence of particular visual appearances and vocalisations). Whilst CZs might incorporate both multi-modal and amodal coding, their reliance upon amodal coding is likely to increase as information from more modalities is included. Thirdly, 'distributed-plus-hub' models also propose direct multi-modal links, but posit a single overarching amodal convergence zone which codes associations between object features across all modalities (e.g., Rogers et al., 2004; Rogers and McClelland, 2004; Patterson et al., 2007; Pobric et al., 2007).

To assist comparisons between these models, they can be situated along a theoretical continuum which varies in the extent to which amodal coding (i) dominates, and (ii) is dissociated from multi-modal representations. In this framework, distributed-only models posit no amodal coding and the action of multi-modal representations, distributed-plus-convergence models posit multiple levels of amodal coding that are increasingly complex and divorced from multi-modal representations, and distributed-plus-hub models posit a unitary level of amodal coding which is dissociated from multi-modal representations. Given that the models can be viewed in this way as gradations along a continuum rather than conflicting alternatives, it is possible that semantic processing might encompass elements from each theory simultaneously. Recently, both theoretical and empirical advances have articulated the advantages of this more moderate

approach (e.g., Pobric et al., 2010a; Crutch and Warrington, submitted). For example, Crutch and Warrington (submitted) envisage a 'coalition model' in which links between object features co-exist at all described levels of representation; thus, a graded (rather than binary) interface between multi-modal and amodal representations is proposed, instantiated within a hierarchy of progressively abstract object representations.

1.5.5.2 Amodal and multi-modal deficits of semantic processing

Evidence for the influence of amodal representations upon semantic processing has been predominantly derived via the study of patients with semantic dementia (SD). SD involves a highly selective degeneration of semantic knowledge that impairs the recognition of objects in all modalities, including spoken and written words, pictures, environmental sounds, smells and touch (Bozeat et al., 2000; Coccia et al., 2004; Luzzi et al., 2007). Additionally, the semantic deficit in SD affects production as well as recognition tasks, including object drawing and object use (Bozeat et al., 2002; Bozeat et al., 2003). Furthermore, detailed investigations have suggested that semantic deficits are of equivalent severity across multiple modalities of input and output (Bozeat et al., 2000). Thus, deficits in SD are most parsimoniously accounted for by an impairment of amodal, rather than multi-modal, semantic processing. Further, since SD patients suffer selective atrophy to a network centred upon the anterior temporal lobes (ATLs; Gorno-Tempini et al., 2004; Schroeter et al., 2007; Rohrer et al., 2009; Seeley et al., 2009; Rohrer et al., 2010b), a substrate for amodal semantic processing mechanisms is suggested. Additionally, convergent evidence for a role of the ATL in amodal semantic processing has been provided by rTMS and fMRI studies in healthy controls (Pobric et al., 2007; Pobric et al., 2010b; Visser et al., 2010b).

Despite the import of amodal processing in object recognition, other neuropsychological evidence suggests that the semantic system also relies upon multi-modal semantic representations. In particular, evidence for this assertion has been taken from patients who exhibit semantic disorders that affect objects either within a particular modality (e.g., visual) or a particular category (e.g., living things). Various theorists have argued that such modality- and category-specific deficits suggest that the semantic system involves a number of dissociable modality- and category-specific substrates, which contain

corresponding multi-modal semantic representations (Warrington and McCarthy, 1983; Warrington and Shallice, 1984; Warrington and McCarthy, 1987; Caramazza and Shelton, 1998; Crutch and Warrington, 2003). It must be noted that other theorists have argued that amodal representations might similarly account for such deficits, for example, if stimuli in certain modalities or categories exhibit particular statistical regularities (e.g. living things have more shared features than non-living things, and are therefore more difficult to differentiate; Devlin et al., 1998). However, more recent studies argue that multi-modal representations are involved, at least to some degree, in semantic processing (Pobric et al., 2010a; Crutch and Warrington, submitted), and it may be argued that modality- and category-specific impairments are more parsimoniously accounted for by multi-modal than amodal processing deficits. Thus, for the purposes of this thesis, it will be assumed that modality- and category-specific object recognition disorders indicate, at least to some extent, the involvement of multi-modal representations in semantic processing.

Modality-specific deficits of semantic processing have been most widely studied in the visual modality, and are indicated by reports of visual associative agnosia, i.e., selective semantic processing deficits for visual stimuli in the context of adequate visual perception (De Renzi et al., 1969; Taylor and Warrington, 1971; Warrington and Taylor, 1978). Further, such deficits have been dissociated from selective impairments of visual apperceptive processing, both cognitively and anatomically (De Renzi et al., 1969; Warrington and Taylor, 1978). Anatomically, visual associative agnosia has been associated with lesions of the left hemisphere (De Renzi et al., 1969; Warrington and Taylor, 1978). Additionally, this disorder has been described following left occipital damage (Fery and Morais, 2003; Anaki et al., 2007), or left occipital and temporal damage (Carlesimo et al., 1998), and it can be argued that the involvement of these substrates is more suggestive of multi-modal than amodal deficits. Additionally, the neuropsychological literature also contains reports of category-specific associative agnosias (e.g., Warrington and McCarthy, 1983; Warrington and Shallice, 1984; Warrington and McCarthy, 1987; Silveri and Gainotti, 1988; Hillis and Caramazza, 1991; De Renzi and Lucchelli, 1994; McKenna and Parry, 1994). Whilst such cases are highly variable both in cognitive and anatomical terms, there is a trend for deficits affecting living things

to follow damage to left anterior, mesial and inferior parts of the temporal lobes, and for deficits affecting non-living things to follow damage to a left fronto-temporo-parietal network (Gainotti, 2004).

Taken together, neuropsychological evidence from studies involving predominantly non-auditory stimuli suggest that semantic processing depends upon the concerted action of amodal representations in the ATLs, and multi-modal representations in more posterior perceptual areas. However, whilst such conclusions align with empirical findings from a range of methodologies (Martin and Chao, 2001; Marinkovic et al., 2003; Binder et al., 2009; Pobric et al., 2010a; Visser et al., 2010b), they are nonetheless a matter of considerable controversy.

1.5.5.3 The case for selective auditory semantic processing deficits

Most evidence for mechanisms of semantic processing has been derived using visual or verbal stimuli, and little is known about analogous mechanisms for non-verbal auditory processing; however, there are prima facie reasons to suspect that auditory semantic mechanisms may show a degree of modality-specificity. Firstly, categories of auditory objects tend to exhibit high levels of acoustic homogeneity (Singh and Theunissen, 2003; Woolley et al., 2005; Elliott and Theunissen, 2009), suggesting the possibility of modality-specific interactions between perceptual and semantic representations. Secondly, cross-modal links triggered by the presentation of auditory objects may differ in strength, importance and direction from those triggered by the presentation of objects in other modalities; for example, voice recognition is more likely to rely upon face information than the converse. Thirdly, certain objects and their constituent perceptual properties may have a pre-eminently auditory existence. For example, some objects cannot be accurately represented in other modalities (e.g., the sound qualities of human voices, bird-song and musical instruments), and others are biased towards a primarily auditory representation (e.g., running water, thunder, cicadas, emergency sirens). Additionally, further objects are differentially dependent upon auditory associations despite being comparably dependent upon visual ones (e.g., birds have characteristic songs, but butterflies do not). For these reasons, the study of

auditory object recognition can play a key role in both (i) determining the generalisability of semantic processing models which have been primarily developed in visual and verbal studies, and (ii) revealing mechanisms of semantic processing that are specific to the auditory modality.

1.5.5.4 Auditory semantic processing deficits: behavioural evidence

Patients with semantic dementia (SD) exhibit deficits for the recognition of auditory objects (Bozeat et al., 2000) as part of a proposed disorder for amodal semantic representation (Patterson et al., 2007; Mayberry et al., 2010; Pobric et al., 2010b); this evidence may therefore suggest that the semantic processing of auditory objects is to some extent dependent upon amodal processing. In addition, evidence for the involvement of multi-modal semantic representations is suggested by rare reports of auditory associative agnosia, i.e., selective deficits for semantic processing in the auditory modality, despite adequate auditory perception (Spreen et al., 1965; Eustache et al., 1990; Peretz, 1996; Garrido et al., 2009; Hailstone et al., 2010). Further, available case reports tend to describe category-specific semantic deficits variously affecting environmental sounds (Spreen et al., 1965), voices (associative phonagnosia: Garrido et al., 2009; Hailstone et al., 2010), and musical melodies (e.g., Eustache et al., 1990; Peretz, 1996). However, in many cases these reports fail to rule out the possibility of contributory perceptual impairments which might account for observed semantic deficits. For example, Spreen et al. (1965) described a selective deficit of environmental sound recognition without aphasia and with preserved recognition and naming of objects in other sensory modalities; however, these authors failed to conduct sufficiently sensitive assessments to exclude an underlying perceptual impairment. Similarly, the purity of purported semantic disorders for the categories of music and voices is debateable given that patients tend to exhibit subtle perceptual impairments (music: Peretz, 1996; Ayotte et al., 2000; voices: Garrido et al., 2009). Furthermore, close associations between auditory semantic and perceptual processes have been suggested by one further neuropsychological study: in a relatively homogeneous group of stroke patients, all subjects with an auditory semantic deficit had additional deficits in at least one perceptual task (Clarke et al., 1996).

Thus, although reports of category-specific auditory associative agnosia provide some indication that the semantic processing of sounds involves multi-modal representations, a detailed examination of cases suggests that such processes might be dependent upon related perceptual processes.

1.5.5.5 Auditory semantic processing deficits: anatomical evidence

Three neuropsychological group studies, involving unselected brain damaged patients and sound-to-picture matching tests, show that patients with damage to the right and left cerebral hemispheres confuse perceptually and semantically related sounds, respectively (Vignolo, 1982; Schnider et al., 1994; Vignolo, 2003). Whilst these results suggest a degree of independence between semantic and perceptual processes, they fail to indicate whether implicated semantic mechanisms involve multi-modal or amodal representations. However, research in patients with SD suggests not only that amodal processes are involved in auditory object recognition, but also that they are located in the anterior temporal lobes (Gorno-Tempini et al., 2004; Schroeter et al., 2007; Rohrer et al., 2009; Seeley et al., 2009; Rohrer et al., 2010b). Additionally, examination of the available reports of category-specific auditory associative agnosia, which may be associated with multi-modal semantic processing, reveals a tendency towards left-sided brain damage although evidence is conflicting (Eustache et al., 1990; Lechevalier et al., 1995; Ayotte et al., 2000). Finally, one group study involving stroke patients with left hemisphere damage (Saygin et al., 2003) used a lesion overlap procedure to directly compare brain areas associated with the recognition of two different categories of sound object, verbal and non-verbal. Generally, results emphasised close associations: strong correlations were found between performance on analogous non-verbal and verbal tasks, and a common anatomical correlate was identified in the left posterior auditory association cortices (superior and middle temporal gyri). However, a relative dissociation between categories was also evident: non-verbal deficits were more strongly associated with damage to the posterior auditory association cortices and the inferior parietal lobe. These results should be interpreted cautiously since only one patient exhibited a deficit for the recognition of non-verbal but not verbal stimuli (initially, the study reported this pattern in two patients, but the further examination of one in a subsequent study

provided evidence for an apperceptive rather than a semantic deficit; Saygin et al., 2010, see also section 1.5.3.4). Nevertheless, given that substrates highlighted in this study were found predominantly within auditory processing areas, results may indicate the influence of multi-modal representations in non-verbal auditory semantic processing. Further, overlapping and dissociated substrates for the two sound categories examined may indicate the presence of both modality- and category-specific multi-modal mechanisms respectively. In combination, however, neuropsychological anatomical evidence provides rather limited insight into substrates of auditory semantic processing.

Taking the behavioural and anatomical evidence together, the neuropsychological literature tentatively indicates the presence of a range of semantic processing mechanisms within the left hemisphere involving either amodal or multi-modal representations. However several factors may indicate that auditory semantic knowledge is distributed and at least partially dependent upon other cognitive (e.g., perceptual) processes: the rarity of selective auditory agnosia, the likely presence of accompanying perceptual deficits, indications of perceptual-semantic interactions, and the lack of clear anatomical correlates.

1.5.5.6 Auditory semantic processing: neuroimaging studies of healthy subjects

1.5.5.6.1 Evidence for the involvement of multi-modal semantic representations

There is an increasing body of evidence from fMRI studies of healthy controls that implicates multi-modal representations in semantic processing, both in auditory and non-auditory modalities. In particular, a rich literature suggests that the neural systems involved in knowing about objects overlaps substantially with those implicated in the perception of objects (within posterior temporal, inferior parietal, and occipital lobes; Martin and Chao, 2001; Martin, 2007). For example, Martin and colleagues (1995) used fMRI to scan healthy subjects whilst they generated the names of either actions or colours typically associated with visual objects (presented as black and white photographs); thinking about actions activated areas implicated in motion perception (posterior middle temporal gyrus), whilst thinking about colours activated areas implicated in

colour perception (inferior temporal gyrus). A wealth of similar studies suggests that the semantic processing of objects from different categories (tools, animals, colours, human actions, faces, houses) is conducted within regions that are similar to those active during their perception (Martin and Chao, 2001; Martin, 2007). Moreover, results suggest that since different object categories depend upon different perceptual processes, multi-modal semantic representations are activated in a category-specific manner. Additionally, throughout this literature, activity corresponding to semantic processes tends to show a distributed topography that overlaps only partially with regions implicated in corresponding perceptual processes (Martin et al., 1995; Martin and Chao, 2001). This evidence indicates that similar cortical areas contain distinct neural systems for the perception and the multi-modal semantic representation of objects; however, given the close association of these systems, the interface between perceptual and semantic representations is likely to be graded rather than binary.

Analogous fMRI studies in the auditory modality have implicated multi-modal semantic representations in auditory object recognition. For example, listening to sounds that form part of the human motor repertoire (e.g., tool sounds, non-vocal human action sounds: Lewis et al., 2005, 2006, 2010; Engel et al., 2009) selectively activates areas associated with dynamic action coding (posterior superior temporal sulcus, posterior middle temporal gyrus), and praxis coding (inferior parietal lobe, inferior frontal gyrus). In contrast, listening to sounds from acoustically homogeneous categories (e.g., animal vocalisations, mechanical sounds: Lewis et al., 2005; Lewis et al., 2006; Engel et al., 2009; Lewis et al., 2010) selectively activates areas for fine-grained auditory perceptual discrimination (auditory association cortices). Similarly, recent work (Engel et al., 2009; Lewis et al., 2010) has provided evidence for the anatomical dissociation of recognition processes corresponding to four different action sound categories (human-produced, animal-produced, mechanical and environmental) within fronto-temporo-parietal regions that are commonly associated with auditory perceptual mechanisms. Taken together, this evidence suggests that auditory object recognition depends upon the category-specific activation of multi-modal semantic representations (e.g., motor information about tool use). Importantly, such findings may account for the cases of

category-specific auditory associative agnosia described in the neuropsychological literature.

1.5.5.6.2 Evidence for interactions between auditory perceptual and semantic processes

As already suggested, there are prima facie reasons to suspect that perceptual and semantic processes exhibit important interactions during auditory object recognition, since semantic sound categories tend to exhibit high levels of perceptual (and acoustic) homogeneity (Singh and Theunissen, 2003; Woolley et al., 2005; Elliott and Theunissen, 2009). Indeed, fMRI studies in healthy subjects have provided empirical support for this claim via the use of experimental conditions that isolate activity associated with different cognitive stages of sound processing, including basic property perception, object apperception and semantic recognition (Engel et al., 2009; Staeren et al., 2009; Lewis et al., 2010; Leaver and Rauschecker, 2010). Firstly, Lewis et al. (2010) asked subjects to rate sound stimuli on three semantic attributes outside the scanner (although it is likely that ratings additionally incorporated perceptual factors): concreteness (extent to which the sound represents a distinct source); effectuality (extent to which the listener could produce or influence the sound); spatial scale (size of the source relative to the listener). Results showed a partial overlap between brain regions involved in apperceptive representation, and brain regions showing parametric sensitivity to one or more of the semantic ratings. Although a causal relationship remains to be verified, these results suggest that regions coding perceptual and semantic object information are overlapping. Similarly, Engels et al. (2009) compared two analogous tasks which taxed perceptual and semantic processing mechanisms to different extents (semantic: subjects were asked to attend to the sound categories; perceptual: subjects merely pushed a button at the start of each sound). Activation across the two tasks was found within similar regions, but with more widespread distribution in the semantic task. Finally, two further studies (Staeren et al., 2009; Leaver and Rauschecker, 2010) isolated activity reflecting a combination of apperceptive and semantic auditory object processing by controlling for basic perceptual properties. In the study by Leaver and

Rauschecker (2010), regions involved in object representation were similar whether or not basic perceptual properties were taken into account. In the study by Staeren et al. (2009), activity relating to object representations traversed regions associated by other studies with both basic property and more complex object perception throughout the auditory cortices. Thus, all of the above studies (Engel et al., 2009; Staeren et al., 2009; Lewis et al., 2010; Leaver and Rauschecker, 2010) suggest, if tentatively, that auditory semantic processing involves similar areas to those implicated in perceptual (property or apperceptive) representation, but with a different topology; this partially overlapping organisation may indicate both a relative dissociation of perceptual and semantic processes, and the presence of important perceptual-semantic interactions.

1.5.5.6.3 Does auditory semantic processing involve amodal representations in the anterior temporal lobes?

As already described, SD patients exhibit auditory object recognition deficits as part of a wider impairment of amodal semantic representation, in association with focal damage to the ATLs (Bozeat et al., 2000). This neuropsychological evidence thereby suggests that amodal processes in the ATL are a necessary component of auditory semantic processing; in contrast, the available fMRI evidence in healthy humans often fails to highlight a role for this region (e.g., Lewis et al., 2005). However, this discrepancy is likely to reflect several methodological issues rather than a real absence of ATL involvement in auditory semantic processing. Firstly, the above cited auditory neuroimaging studies tend to employ tasks (or passive listening paradigms) that may emphasise perceptual over semantic processes, and are therefore likely to trigger more activation in multi-modal than amodal processing regions. Secondly, for several practical reasons it is notoriously difficult to detect activity changes in the ATLs using fMRI: their extreme anterior location means that they are often ‘missed’, and their proximity to a range of different tissue types (bone, air) makes them susceptible to distortion artifacts (Visser et al., 2010b). However, recent fMRI studies that account for these issues reveal robust activity during semantic processing in an inferior region of the bilateral ATLs (Visser et al., 2010a; Visser and Lambon Ralph, 2011); further, activity in this

region is equivalent for stimuli presented in different modalities (written verbal, auditory verbal, auditory non-verbal, visual), thus indicating the presence of amodal processes. Additionally, the technique of rTMS does not suffer from similar methodological problems, and a range of healthy subject studies in non-auditory modalities strongly implicate the ATLs in semantic processing (Pobric et al., 2007; Pobric et al., 2010b). Whilst analogous studies in the non-verbal auditory modality using fMRI or rTMS are yet to be conducted, similar findings would be predicted. Thus, it can be argued that the neuroimaging literature of auditory semantic processing in healthy controls does not rule out contributions from amodal processing in the ATLs.

1.5.5.7 Semantic processing deficits: section summary

To summarise, auditory object recognition is likely to rely upon a combination of perceptual, multi-modal semantic and amodal semantic mechanisms distributed predominantly throughout temporal and parietal regions. The auditory neuropsychological literature tentatively supports this suggestion. For example, amodal mechanisms are indicated by auditory recognition deficits in SD. Additionally, multi-modal mechanisms dedicated to particular sound categories are indicated by cases of category-specific auditory associative agnosia. However, the general infrequency of selective auditory associative agnosia, along with the lack of any clear anatomical correlate, may indicate that auditory semantic processing is particularly dependent upon interactions with perceptual processes. fMRI and rTMS studies in healthy subjects support the view that auditory object recognition depends upon the concerted action of perceptual, multi-modal semantic and amodal semantic representations. Further, they also suggest that auditory object recognition may be particularly dependent upon interactions between perceptual and semantic processes. Additionally, this assertion aligns with the natural structure of sounds, which tend to exhibit high correlations between perceptual and semantic characteristics. Overall, auditory object recognition may occur through the action of a large distributed neural network throughout temporo-parietal cortices, with continuous gradations of perceptual, multi-modal semantic and amodal semantic representations arranged in an overlapping fashion. Such a network would include regions of

modality- and category-specificity, together with regions that represent knowledge in amodal form.

1.5.5.8 Semantic processing deficits in dementia

The semantic processing of auditory objects has been studied relatively infrequently in dementia. As already indicated, it is proposed that SD involves the deterioration of a temporal lobe network for amodal semantic representation, and empirical evidence shows that behavioural deficits extend to the auditory modality (Bozeat et al., 2000; Seeley et al., 2009). However, further dementia syndromes involving selective damage to distinct functional networks are also likely to produce impairments of auditory semantic processing. For example, AD is associated with a semantic deficits in multiple modalities (e.g., Nebes, 1989; Thompson-Schill et al., 1999; Grossman et al., 2003; Chertkow et al., 2008), and limited empirical evidence already implicates the recognition of auditory objects (Jeon and Lee, 2009; Baird and Samson, 2009; Vanstone and Cuddy, 2010); however, the cognitive basis of these deficits is unclear, and may reflect deficits of semantic access as well as semantic representation (Nebes, 1989; Chertkow and Bub, 1990; Hodges et al., 1992; Greene and Hodges, 1996b; Saykin et al., 1999; Joubert et al., 2010). Additionally the syndromes of AD, PNFA and LPA involve deterioration of temporal and parietal regions which are implicated by studies of healthy subjects in multi-modal semantic representation. Thus, present investigations will compare auditory semantic processing in SD, AD, PNFA, and LPA. Given that each syndrome involves distinct patterns of distributed damage, the comparison of behavioural results may help to illuminate the cortical organization of corresponding functional networks.

1.6 Selection of dementia patient populations

As already described, the dementias are a group of neurological diseases involving non-random and selective anatomical damage to functionally coherent neural networks (Sonty et al., 2007; Seeley et al., 2009; Mesulam, 2009; Zhou et al., 2010), and corresponding cognitive decline (see Rossor et al., 2010). Further, particular dementia syndromes target distinct networks, producing unique profiles of cognitive impairment. Of particular relevance to the present study, the anatomical and neuropsychological signatures of four dementia syndromes may indicate contrasting profiles of non-verbal auditory processing deficits. These syndromes are typical Alzheimer's disease (AD), and three subtypes of primary progressive aphasia (PPA): semantic dementia (SD), progressive non-fluent aphasia (PNFA), and logopenic (phonological) aphasia (LPA). Proposed investigations will therefore comprise the auditory neuropsychological assessment of patients with SD, PNFA, LPA and AD; these syndromes will now be described in more detail.

1.6.1 Semantic dementia (SD)

1.6.1.1 General neuropsychology

Neuropsychologically, SD is defined by the gradual and selective deterioration of semantic knowledge. Initially, this deficit tends to affect the processing of words (Hodges and Patterson, 2007) and patients commonly present with speech that is fluent but circumlocutory, empty of meaning, and full of indefinite terms (e.g., 'thing') in place of more precise and meaningful words (Bonner et al., 2010). Despite this focus on language, the deterioration of semantic knowledge in SD is pan-modal, involving non-verbal modalities such as vision, sound, smells and touch (Bozeat et al., 2000; Coccia et al., 2004; Luzzi et al., 2007). Additionally, the semantic deficit in SD affects production as well as recognition tasks, including object drawing and object use (Bozeat et al., 2003; Bozeat et al., 2002). Furthermore, detailed investigations suggests that semantic deficits are of equivalent severity across multiple modalities of input and output (Bozeat et al., 2000). In view of this evidence, it has been argued that observed deficits reflect the deficient representation of knowledge in an abstract 'amodal' code that can

interact with processes in any modality (Hodges and Patterson, 1996; Patterson et al., 2007; Mayberry et al., 2010; Pobric et al., 2010b). Additionally, a growing literature suggests that patients with SD show impaired performance during certain 'non-semantic' tasks including visual apperception (Hovius et al., 2003; Ikeda et al., 2006; Caine et al., 2009); however, it is argued that such findings are more likely to reflect the indirect effects of a core semantic processing disorder than additional separate deficits. For example, apperceptive tasks often depend, to some extent, upon intact semantic knowledge; thus, semantic deterioration in SD may lead to impaired interactions between semantic and apperceptive processes, which give rise to apperceptive deficits (Ikeda et al., 2006). Despite this evidence, SD is generally associated with the marked preservation of most non-semantic cognitive functions (at least initially), including a range of perceptual and visuo-spatial processes, episodic memory, and executive functioning (e.g., Hodges and Patterson, 1996).

1.6.1.2 Auditory neuropsychology

A range of neuropsychological studies have provided direct evidence that the proposed amodal object recognition deficit in SD extends to the auditory modality; available evidence details impaired processing of environmental sounds (Bozeat et al., 2000) and familiar voices (Gainotti et al., 2003). In contrast, given that SD is generally associated with preserved perceptual processing (commonly assessed in verbal and visual modalities), it might be suggested that patients would show normal abilities of auditory property perception, apperception, and scene analysis; however, empirical data to support this claim are currently unavailable.

1.6.1.3 General neuroanatomy

Anatomically, structural imaging shows that the initial stages of SD lead to bilateral but leftward biased atrophy throughout ventral and lateral regions of the anterior temporal lobes (ATLs), the anterior hippocampus and the amygdalae (e.g., Gorno-Tempini et al., 2004; Schroeter et al., 2007; Rohrer et al., 2009; Rohrer et al., 2010b). Longitudinal imaging shows that temporal atrophy in SD progressively affects additional regions including the superior temporal cortex, and homologous regions of the right hemisphere. Additionally, functional imaging shows abnormal activity in posterior temporal regions including the inferior temporal lobe (Mummery et al., 1999). Further, diffusion tensor imaging

(DTI) analyses have found evidence for damage to the white matter tracts connecting the anterior temporal cortex with other brain regions (e.g., Agosta et al., 2010).

1.6.1.4 Auditory neuroanatomy

A variety of healthy subject fMRI studies have associated regions that are damaged in SD with mechanisms of object recognition. For example, a direct correspondence between the profile of atrophy in SD and a network for object processing in the healthy brain has been demonstrated (Seeley et al., 2009). Although it is notoriously difficult to detect fMRI signals in the most prominent site of disease involvement in SD, the ATLs, recent studies implicate this region in verbal and visual object recognition (e.g., Visser et al., 2010a, Pobric et al., 2010b); although analogous studies in the auditory modality are yet to be conducted, similar findings would be predicted. Furthermore, many of the posterior temporal areas that are functionally disrupted in SD have been associated with auditory object recognition processes that depend upon multi-modal semantic representations (i.e., those involving information coded within particular modalities, see section 1.5.5.1; Lewis et al., 2005; Lewis et al., 2006; Engel et al., 2009; Lewis et al., 2010). Together, this evidence suggests an anatomical basis for deficits of auditory object recognition in SD, caused by a combination of multi-modal and amodal semantic processing impairments.

1.6.1.5 The predicted auditory deficit profile of SD

To summarise, SD appears to involve the selective degeneration of brain regions corresponding to an object recognition network in the temporal lobes of the healthy brain. Of relevance here, patients show impairments of non-verbal auditory semantic processing, and damage to regions associated with corresponding amodal and multi-modal semantic mechanisms in the healthy brain. Thus, appropriate assessments of SD may illuminate the organisation of the auditory object recognition network.

1.6.2 Progressive non-fluent aphasia (PNFA)

1.6.2.1 General neuropsychology

Most PNFA patients present with dysfluent and effortful speech, often involving numerous pauses and errors. For example, a recent study has shown that

speech rate in PNFA typically reduces to between a third and a half of the normal rate (Ash et al., 2010). Additionally, the majority of speech errors (~80%) tend to involve real but incorrectly used phonemes whilst a minority (~20%) consist of non-speech sounds (Ash et al., 2010); this pattern suggests combined deficits of phonological word assembly and motor speech production. Phonological word assembly impairments can also explain observed dissociations between different language tasks: for example, patients show deficient confrontation naming despite intact reading, which might be accounted for by a reduced level of phonological support in the former task (Croot et al., 1998). Additionally, evidence suggests that PNFA also leads to grammatical processing impairment (Rhee et al., 2001; Peelle et al., 2008), which may manifest as reduced sentence comprehension. However, this particular impairment may also reflect a co-morbid deficit of verbal working memory, which is particularly relevant to the processing of long-distance syntactic relationships (Grossman et al., 2005). Despite this array of deficits, PNFA patients show relative sparing of abilities for single word and object comprehension, which suggests an intact semantic memory and helps to differentiate the syndrome from SD. Thus, PNFA includes impairments of phonological representation, motor articulation of speech, grammatical processing and verbal working memory, all of which are manifest in patients' dysfluent and effortful speech (Grossman and Ash, 2004; Bonner et al., 2010).

1.6.2.2 Auditory neuropsychology

Selective deficits for the perception of words presented in the auditory modality have been reported in cases of unspecified PPA resembling PNFA (Otsuki et al., 1998; Iizuka et al., 2007; Jorgens et al., 2008). Whilst such deficits may signal the presence of a disorder specific to the verbal modality, the acoustic homogeneity of verbal sounds alternatively raises the possibility of an underlying non-verbal auditory impairment that particularly affects the perception of words. Indeed, this hypothesis gains empirical support from at least one of these studies, which reported temporal resolution deficiencies underlying an impairment of word perception (Otsuki et al., 1998). Additionally, further PNFA-like cases have been described with agnosia for non-verbal sounds as a leading feature (Confavreux et al., 1992; Kaga et al., 2004; Yamamoto et al., 2004). Thus, limited evidence supports the view that PNFA

may involve primary non-verbal auditory perceptual deficits that particularly impair the perception of words, but which may also affect the processing of other sound objects with complex spectrotemporal structures.

1.6.2.3 General neuroanatomy

PNFA involves bilateral but left-biased cortical damage surrounding the Sylvian fissure; specific regions involved include the inferior frontal gyrus, the dorso-lateral prefrontal cortex, the insula, and a large extent of the superior temporal cortex spreading caudally into the parietal lobe (Gorno-Tempini et al., 2004; Schroeter et al., 2007; Rohrer et al., 2009; Rohrer et al., 2010b; Hu et al., 2010). A direct overlap between this profile of atrophy and the peri-Sylvian network for language processing in healthy controls has been demonstrated, thus providing an anatomical basis for patients' aphasia (Seeley et al., 2009). In particular, structurally (Gorno-Tempini et al., 2004) and functionally (Jorgens et al., 2008) damaged areas of the superior temporal lobe correspond to those normally involved in the perceptual processing of complex speech sounds (Rauschecker, and Scott, 2009). Additionally, damaged posterior temporo-parietal regions (including the planum temporale, PT) have been implicated by healthy subject fMRI studies in bi-directional auditory-motor transformations required during speech (Warren et al., 2005b). Finally, structural imaging of patients has shown associations between impaired grammatical comprehension and left inferior frontal atrophy (Peelle et al., 2008), and between dysfluency and left interior frontal and superior temporal atrophy (Ash et al., 2009; Gunawardena et al., 2010).

1.6.2.4 Auditory anatomy

Although links between cortical damage and deficient language functions are emphasized, the profile of atrophy in PNFA also indicates impairments of non-verbal sound processing. For example, fMRI studies of healthy subjects associate sub-regions of the superior temporal lobe damaged in PNFA not only with the perceptual representation of speech but also with the perceptual representation of auditory properties and non-verbal auditory objects (Staeren et al., 2009; Leaver and Rauschecker, 2010). Additionally, further studies associate posterior temporo-parietal regions (including the PT), atrophied in PNFA with the segregation of complex auditory mixtures into constituent sound objects (i.e., auditory scene analysis; Griffiths and Warren, 2002; Smith et al.,

2010), and the processing of multi-modal semantic representations necessary for the recognition of imitable action sounds (Lewis et al., 2005; Lewis et al., 2006; Engel et al., 2009; Lewis et al., 2010).

1.6.2.5 The predicted auditory deficit profile of PNFA

To summarize, PNFA appears to involve the selective degeneration of brain regions corresponding to a peri-Sylvian network for both verbal and non-verbal auditory processing in the healthy brain. Whilst neuropsychological evidence is at present limited, several patient reports provide preliminary evidence that PNFA leads to non-verbal auditory perceptual impairments. Furthermore, anatomical evidence suggests that the syndrome could lead to a range of auditory deficits involving perceptual, apperceptive and multi-modal semantic processes, and auditory scene analysis. Additionally, evidence for working memory deficits in PNFA suggest that patients may show greater non-verbal auditory impairments during the processing of sounds that impose higher working memory loads. Thus, appropriate assessments of PNFA may illuminate cortical networks for a range of non-verbal auditory processes.

1.6.3 Logopenic (phonological) aphasia (LPA)

In contrast to other PPA syndromes, LPA is commonly underpinned by AD pathology (Rohrer et al., 2010d). However, at early disease stages, AD involves prominent episodic memory complaints whilst LPA is characterised by language deficits. Further, atrophy in AD affects both hemispheres equally, whilst LPA patients tend to show greater left-sided damage. Thus, LPA is associated with a distinctive neuropsychological and anatomical profile, and may be considered a ‘left-hemisphere variant’ of AD (Rohrer et al., 2010d).

1.6.3.1 General neuropsychology

LPA is characterised by fluent but sparse speech containing prolonged pauses and phonemic errors; detailed neuropsychological investigations indicate that underlying these deficits is a combination of anomia and phonological processing impairments (Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2011; Rohrer et al., 2010c). Additionally, patients perform poorly on auditory span tasks (including digit, word and letter versions), indicating a prominent verbal working memory impairment (Gorno-Tempini et

al., 2008). In further support of this particular memory deficit, patients also show a relatively greater impairment for sentence compared to single word processing, during both comprehension and repetition tasks. Differentiation from the other PPA syndromes is assisted by the observations that LPA patients initially show preserved grammatical processing and an absence of motor speech difficulties (in contrast to PNFA) and intact single word comprehension (in contrast to SD); additionally, patients also exhibit comparatively poorer episodic memory and calculation deficits than both PNFA and SD. It has been suggested that verbal working memory deficits might account for much of the cognitive impairment in LPA (Gorno-Tempini et al., 2008); however, in view of the wide range of disrupted processes, including deficits of single word and grammatical comprehension at later stages, it is more likely that impairments are caused by a range of underlying factors (Rohrer et al., 2010c).

1.6.3.2 Auditory neuropsychology

Whilst LPA patients have yet to be studied within the framework of auditory neuropsychology, limited evidence from cases of unspecified PPA resembling LPA suggests deficits of non-verbal auditory object processing (Kuramoto et al., 2002; Uttner et al., 2006); however, these studies do not specify the cognitive locus of impairments as perceptual, semantic or otherwise. Additionally, to the extent that the verbal working memory deficit observed in LPA reflects damage to mechanisms shared between modalities, patients may show greater auditory impairments for processing sounds that extend in time and thereby impose higher working memory loads.

1.6.3.3 General neuroanatomy

As in PNFA, LPA involves left-biased atrophy of posterior superior temporal and inferior parietal regions (Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2008; Rohrer et al., 2010b; Grossman, 2010) which overlap with the peri-Sylvian language network, providing an anatomical basis for patients' aphasia. However, left temporo-parietal regions are more prominently involved in LPA than in PNFA (Gorno-Tempini et al., 2008; Wilson et al., 2009; Rohrer et al., 2010b). In particular, further neuropsychological evidence suggests that damage to the inferior parietal cortex may account for the prominence of verbal working memory impairments in LPA (e.g., Baldo and Dronkers, 2006).

1.6.3.4 Auditory neuroanatomy

As suggested in relation to PNFA, damage to peri-Sylvian temporal and inferior parietal regions indicates that LPA patients may suffer prominent deficits of non-verbal auditory processing. For example, damaged superior temporal regions include those associated in healthy controls with the perception of auditory properties and objects. Additionally, the involvement of posterior temporal-parietal regions (including the planum temporale) might indicate deficits of both auditory scene segregation (Griffiths and Warren, 2002; Smith et al., 2010), and the processing of multi-modal semantic representations necessary for the recognition of imitable action sounds (Lewis et al., 2005; Lewis et al., 2006; Engel et al., 2009; Lewis et al., 2010).

1.6.3.5 The predicted auditory deficit profile of LPA

Although previous auditory neuropsychological assessments in LPA are limited, preliminary behavioural evidence suggests that patients may suffer non-verbal auditory impairments; furthermore, anatomical data indicates potential substrates for such impairments. For example, LPA involves the selective degeneration of brain regions corresponding to a peri-Sylvian network for both verbal and non-verbal auditory processing in the healthy brain; thus, LPA is likely to cause a range of non-verbal auditory processing deficits affecting perceptual, apperceptive and semantic stages of cognition. However, posterior temporo-parietal regions are more prominently involved in LPA than in other PPA syndromes; thus, patients may exhibit particular impairments for apperceptive processing, auditory scene analysis and the representation of multi-modal semantic information required for the recognition of imitable action sounds. Finally, prominent working memory deficits in LPA suggest that patients may show greater non-verbal auditory impairments during the processing of sounds that impose higher working memory loads. Thus, appropriate assessments of LPA may illuminate mechanisms of non-verbal auditory processing, as well as interactions between such mechanisms and relevant executive functions such as working memory.

1.6.4 Progranulin associated aphasia (GAA)

1.6.4.1 General neuropsychology and neuroanatomy

Although SD, PNFA and LPA have been neuropsychologically and anatomically differentiated, clinical experience suggests that not all PPA patients align with one of these syndromes; thus, further work is required to describe additional syndromes and refine the nosology of PPA. In particular, recent work has described PPA patients with a unique combination of clinical features in association with mutations to the progranulin (GRN) gene, thus indicating the presence of a distinct syndrome which has been referred to as 'progranulin associated aphasia' (GAA; Rohrer et al., 2010a; Rohrer et al., 2010c). The anatomical and neuropsychological profile of GAA bears some resemblance to LPA, including damage to a comparable temporo-parietal network in association with similar language deficits (sparse, slow and impoverished spontaneous speech with long word-finding pauses, impaired verbal working memory, impaired sentence processing) and non-linguistic impairments associated with parietal damage (dyscalculia). However, these patients also exhibit a number of distinctive neuropsychological features including impairments of single word comprehension and single word repetition (Rohrer et al., 2010c). Moreover, recent work has described a single GAA case who exhibited a highly asymmetric neuropsychological profile involving widespread dominant hemisphere (verbal) and parietal (dyslexia, dysgraphia, dyscalculia) impairments, but preserved non-dominant functions including performance IQ, pictorial episodic memory, visuo-spatial working memory and visual object perception (Rohrer et al., 2010a).

1.6.4.2 The predicted auditory deficit profile of GAA

In view of the partial overlap between syndromes, GAA and LPA might lead to similar non-verbal auditory impairments; however, the strongly asymmetric neuropsychological profile of GAA may lead to syndrome-specific deficits. In particular, the assessment of patients with GAA is likely to facilitate inferences about the relative involvement of verbal and non-verbal processes in non-verbal auditory cognition. However, given the current lack of evidence, no specific hypotheses about the auditory performance of patients with GAA will be suggested here.

1.6.5 Typical Alzheimer's Disease (AD)

1.6.5.1 General neuropsychology

AD patients initially present with problems of episodic memory, including repetitive questioning, misplacement of items, and an inability to recall contextual details of events (Rossor et al., 2010). In the earliest stages, patients may show objective episodic memory deficits (recall worse than recognition), without other cognitive impairments (e.g., Moss et al., 1986; Coen et al., 1997); this profile provides a basis for the differentiation of AD from PPA. However, patients latterly develop cognitive deficits that are widespread (Storey et al., 2002; Rossor et al., 2010), implicating faculties of working memory (e.g., Rochon et al., 2000), visual object perception (Fujimori et al., 1997; Adduri and Marotta, 2009), and semantic memory (Chertkow and Bub, 1990; Greene and Hodges, 1996a; Greene and Hodges, 1996b). Whilst evidence suggests that the semantic impairment in AD is pan-modal, it is likely to reflect deficits of semantic access as well as semantic representation (Nebes, 1989; Chertkow and Bub, 1990; Hodges et al., 1992; Greene and Hodges, 1996b; Saykin et al., 1999; Joubert et al., 2010). Additionally, the semantic and working memory difficulties in AD appear to contribute to various language problems including empty but fluent speech, and impaired auditory and written verbal comprehension; however, in contrast to PNFA and LPA, grammatical and phonological processes are relatively intact at early disease stages (Storey et al., 2002).

1.6.5.2 Auditory neuropsychology

A significant behavioural literature provides evidence for a relatively broad range of non-verbal auditory deficits in AD. For example, patients show impaired processing of certain relatively simple auditory properties (duration: Kurylo et al., 1993; Hellstrom and Almkvist, 1997), but preserved perception of others (pitch: Kurylo et al., 1993). However, such property processing deficits are reported relatively infrequently, and auditory impairments in AD more commonly involve the representation of complex objects, thus mirroring similar findings in the visual modality (Adduri and Marotta, 2009). Specifically, AD has been associated with the impaired perceptual processing of various auditory objects including words (Eustache et al., 1995), environmental sounds (Rapcsak et al., 1989, Eustache et al., 1995), and emotions conveyed by

prosodic patterns (Testa et al., 2001). Additionally, evidence for a pan-modal semantic processing deficit in AD (Greene and Hodges, 1996a), suggests that auditory object recognition may also be impaired. Indeed, AD has been associated with semantic impairments affecting the recognition of environmental sounds (Jeon and Lee, 2009), and melodies (Baird and Samson, 2009; Vanstone and Cuddy, 2010). In addition, clinical experience suggests that AD patients commonly report difficulties with following conversations in the presence of background noise or over a noisy telephone line; such observations might indicate a deficit of auditory scene analysis. Empirical evidence supports this claim, demonstrating that both early and pre-symptomatic AD patients show impairments on 'sentence competition' tasks which require attention to one of two simultaneously presented sentences (Gates et al,. 1996; Gates et al,. 2002; Gates et al., 2008). Although not yet tested, such data may reflect an underlying auditory scene analysis (ASA) deficit, affecting verbal and non-verbal stimuli alike.

1.6.5.3 General neuroanatomy

Anatomically, AD is associated with bilateral and symmetrical atrophy that is initially most prominent in the hippocampus but which later incorporates parahippocampal regions and the temporal lobes more widely, as well as the parietal and frontal lobes (e.g., Whitwell and Jack, 2005). Recent evidence has shown a direct correspondence between this profile of atrophy and a functionally coherent 'default network,' (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010), which is particularly active when individuals are engaged in internally directed cognitive tasks including remembering autobiographical details (episodic memory), and constructing representations of possible or imagined scenarios (e.g., when thinking about the future or other people's perspectives; Buckner et al., 2008).

1.6.5.4 Auditory neuroanatomy

The profile of cortical damage in AD encompasses a range of temporal and parietal regions that are associated in the healthy brain with various non-verbal auditory processes, encompassing perceptual, apperceptive and semantic stages of cognition. Additionally, electrophysiological studies show altered cortical function during tasks relevant to auditory scene analysis (ASA; e.g., auditory 'oddball' detection) in both pre- and post symptomatic AD groups

(Golob et al., 2007; Golob et al., 2009). Thus, structural and functional damage in AD provides an anatomical basis for a range of non-verbal auditory deficits.

1.6.5.5 The predicted auditory deficit profile of AD

To summarize, evidence in AD indicates the presence of a range of auditory deficits, including perceptual, apperceptive and semantic stages of cognition, which may be associated with damage to various temporal and parietal brain regions. Additionally, the syndrome may lead to prominent ASA impairments following damage to posterior temporo-parietal areas. Further, evidence for working memory deficits in AD suggest that patients may show greater non-verbal auditory impairments during the processing of sounds that impose higher working memory loads. Whilst the auditory deficit profile of AD may therefore overlap with that of PPA, it arises following damage to a highly distinct functional network; from this perspective, auditory assessment in AD may provide not only useful insight into networks for non-verbal auditory processing, but also a useful syndrome against which to compare PPA.

1.6.6 SD, PNFA, LPA and AD contrasted

Considered together, the four syndromes of SD, PNFA, LPA and AD are likely to involve contrasting profiles of non-verbal auditory impairment and cortical damage. Given the cortical (rather than sub-cortical) locus of atrophy, and the relative preservation of primary and secondary auditory cortices (Dekosky and Lopez, 2007; Kipps and Hodges, 2007), the analysis of more basic auditory perceptual properties (e.g., pitch, auditory size) is likely to be preserved. However, PNFA, LPA and AD are all likely to lead to a wide range of deficits involving the analysis of relatively more complex perceptual properties (e.g., timbre), together with impairments of apperceptive and semantic auditory object processing. Additionally, each of these syndromes might involve impairments of auditory scene analysis; however, given previous neuropsychological and anatomical data, such impairments might be most prominent in LPA and AD. In AD, the neuropsychological evidence suggests that perceptual deficits tend to affect the processing of auditory objects rather than auditory properties. In LPA, previous data might indicate a syndrome-specific interaction of non-verbal auditory processing and working memory deficits. Finally, auditory semantic processing impairments may be particularly severe in AD and SD, although

underlying mechanisms may vary. Therefore, it is predicted that the comparison of these overlapping but contrasting profiles of behavioural impairments and cortical damage may illuminate the organisation of networks for non-verbal auditory processing.

1.7 General hypotheses of current investigations

The consideration of the four main dementia syndromes under current investigation (SD, PNFA, LPA, AD) alongside the above presented review of non-verbal auditory processing (section 1.5) leads to eight broad hypotheses which are presented below (the chapters within which each hypothesis is investigated are indicated in brackets).

1. SD, AD, PNFA, and LPA may be characterized by preserved pitch perception given the relative sparing of primary and secondary auditory cortices. However, pitch perception is likely to show a particular reliance upon non-auditory executive processes; thus, dementia syndromes that typically involve executive impairments (e.g., LPA, and to a lesser extent, PNFA and AD) may lead to deficits during pitch perception tasks that impose significant executive demands (Chapters 3, 4).

2. SD, AD, PNFA, and LPA may be characterized by preserved perception of basic auditory size cues, given the sparing of sub-cortical auditory pathways. However, these syndromes may lead to more complex deficits of size representation (e.g., relative magnitude representation, audio-visual matching, perceptual normalization), following damage to auditory association and parietal cortices (Chapter 3).

3. AD, PNFA, and LPA may lead to a heterogeneous range of dystimbrias following distinct profiles of damage to auditory association cortices; such deficits would reflect relatively broad spectral, temporal and/or spectrotemporal processing deficits (Chapters 2, 3, 4).

4. AD, PNFA, and LPA may lead to a heterogeneous range of apperceptive agnosias following distinct profiles of damage to association auditory cortices. Damage within sub-regions of posterior-dorsal auditory cortices implicated in spectral, temporal, and/or spectrotemporal encoding may lead to apperceptive deficits for certain sound categories with corresponding spectrotemporal structures. In contrast, damage focussed upon the planum temporale (PT) might selectively impair auditory template processing, leading to a category-general apperceptive agnosia. Finally, damage within particular sub-regions of

antero-ventral auditory association cortices that show functional specialisation for the processing of particular sound categories may lead to category-specific apperceptive agnosias, whilst more widespread atrophy throughout this region may cause category-general apperceptive deficits (Chapters 2, 3, 4, 5).

5. SD, AD, LPA, and PNFA may lead to semantic processing deficits in the auditory modality, although deficits are likely to be most prominent in SD and AD. In each patient group, semantic deficits are likely to reflect distinct profiles of neuropsychological impairment (e.g., involving multi-modal or amodal semantic representation) following distinct patterns of anatomical damage within auditory association and extra-temporal cortices (Chapters 2, 3, 4, 5).

6. All four dementia syndromes (AD, PNFA, LPA, SD) may involve interactions between auditory perceptual and semantic deficits in reflection of close associations between these processing stages (Chapters 2, 3, 4, 5).

7. AD may lead to ASA deficits following damage to temporo-parietal cortical regions including the PT (Chapter 6).

8. In LPA, prominent working memory deficits may interact with non-verbal auditory processing deficits to produce a syndrome-specific pattern of impairments (Chapters 3, 4).

In view of the lack of evidence, no specific hypotheses about the auditory deficit profile of patients with GAA are offered here. However, given that patients tend to show strongly asymmetric (impaired verbal, preserved non-verbal) neuropsychological profiles, non-verbal auditory assessment may facilitate inferences about the involvement of verbal processes in non-verbal auditory cognition.

The investigations of this thesis will seek to test each of these hypotheses using neuropsychological auditory assessments and neuroimaging techniques. It is hoped that findings will provide insight into both the taxonomy of non-verbal auditory deficits and corresponding mechanisms in the healthy brain.

2 Non-verbal auditory object processing in dementia: study 1

2.1 Summary

This study comprises an investigation of non-verbal auditory processing in a consecutive series of 20 patients with primary progressive aphasia [12 with progressive non-fluent aphasia, PNFA; 8 with semantic dementia, SD]. A preliminary novel experimental neuropsychological battery was designed to examine separately property, apperceptive, and semantic stages of cognition. Within-modality response procedures were employed to minimize extraneous cognitive demands upon patients, and analogous tests were conducted in the visual modality to reveal modality-specific effects. Patients with primary progressive aphasia had deficits of non-verbal sound processing compared with healthy age-matched controls. Specifically, PNFA was associated with predominant auditory perceptual processing deficits in association with damage to a posterior peri-Sylvian network; in contrast, SD was associated with predominant semantic deficits in association with damage to an anteriorly-directed temporal lobe network. These findings argue for the existence of core disorders of non-verbal auditory processing in primary progressive aphasia, and specific disorders at perceptual and semantic levels of cortical auditory processing in PNFA and SD respectively. Data therefore support the relative cognitive and anatomical independence of perceptual and semantic mechanisms implicated in non-verbal auditory sound processing. However, further analyses in both patient groups suggested that associations between property processing, apperceptive and semantic deficits occurred in the context of damage to functionally coherent and wide-spread networks; data thus support the notion that non-verbal auditory processing is conducted within distributed and reciprocally connected cortical networks traversing the superior temporal lobes.

2.2 Aims of the investigation

The aims of this investigation were twofold. The first aim was to design a preliminary non-verbal auditory neuropsychological battery, suitable for the assessment of neurological patients, and including tests to examine property, apperceptive, and semantic processing. The second aim was to use the battery to conduct an initial exploratory investigation of auditory processing deficits in the two canonical primary progressive aphasia (PPA) syndromes: progressive non-fluent aphasia (PNFA) and semantic dementia (SD).

2.3 Non-verbal auditory neuropsychological battery design

2.3.1 Previous non-verbal auditory neuropsychological batteries

Whilst various non-verbal auditory neuropsychological batteries are already available, none involves a comprehensive assessment of each of the auditory processing stages relevant to the current study, in a format that would be suitable for cognitively impaired patients. For example, the temporal subtests of the Newcastle Auditory Battery assess the perception of relevant auditory properties including AM, FM, gap detection and iterated ripple noise detection (Griffiths et al., 2001). However, constituent tests are designed to provide full psychometric functions of individual subject performances, resulting in a lengthy battery (2-3 hours) that most neurological patients would not tolerate. Additionally, other batteries examine more than one auditory process but do not assess all stages relevant to the current study in parallel (e.g., semantic object processing, Bozeat et al., 2000; tests of apperceptive and semantic processing and auditory scene analysis, Clarke et al., 1996). Therefore, current investigations will require the development of a novel auditory neuropsychological battery including assessments of all relevant stages, suitable for use in clinical populations. However, this process will face a number of significant practical challenges which will now be described.

2.3.2 Challenges of non-verbal auditory neuropsychological battery design

Auditory neuropsychological test design options are generally more limited than those available in other modalities. For example, verbal and visual assessments often present arrays of multiple objects from which patients select a response, and this method reduces requirements for patients to hold information in working memory. Unfortunately, this common technique cannot be adopted in the auditory modality because it is generally undesirable to present more than one auditory object simultaneously (except in tests of auditory scene analysis where this is a requirement). Thus, auditory tests often use comparisons between sequentially presented sounds (henceforth sequential sound comparison; e.g. Clarke et al., 1996, Griffiths et al., 2001); however, such paradigms impose additional attentional and working memory loads and therefore may not be ideal for cognitively impaired patients.

As an alternative, some auditory tests involve the cross-modal matching of sounds to arrays of words or pictures (henceforth cross-modal matching, e.g., Bozeat et al., 2000, Clarke et al., 1996), which helps to reduce demands upon attention and working memory. Additionally, via this method it is possible to probe deficits in some detail; for example, the careful design of response options may enable differentiation between semantic and perceptual errors. However, cross-modal tests also have associated problems. In particular, results are more difficult to interpret if processing in the secondary modality is deficient, although in some cases a comparison of analogous tests using three or more modalities may enable the isolation of an auditory deficit (e.g., sound-picture, sound-word, picture-word; see Bozeat et al., 2000). Nevertheless, a more fundamental problem with cross-modal matching tests is that many auditory objects lack precise equivalents in other modalities. For example, it is difficult to find a clear visual representation of the sound of rain, and the use of approximate equivalents (e.g., an umbrella or rain against a window pane) may introduce additional demands on executive processing. Furthermore, even where equivalents in different modalities exist, they may not be well matched for familiarity (compare the familiarity of auditory and visual representations of a cicada).

One further option is to develop tests that involve listening to a single auditory stimulus per trial, and responding according to a forced-choice criterion (henceforth individual sound categorisation). For example, subjects could be asked to report whether individual non-verbal human vocalisations emanate from a male or a female. Notably, this design format relies upon the existence of a suitable sound feature that can be detected and categorised. However, not all auditory properties can be assessed in this manner, since many are not easily labelled, and furthermore, a requirement for verbal labelling may be undesirable in the context of aphasia. Additionally, it is difficult to probe subtle deficits using such neuropsychological paradigms, since there are reduced possibilities for the parametric variation of stimulus properties.

One further practical problem in the making of auditory tests is that sounds are not instantaneous but generally evolve over a time period, the length of which may vary widely (compare the sound of waves with the sound of a stapler). Practically, therefore, it is difficult to equate natural sound stimuli within any given test for duration, although attempts may be made to balance constituent test conditions. Additionally, it can be argued that confounds of memory are inherently present in auditory assessments, to the extent that the integration of information across the duration of a sound is required; this is particularly problematic if patients show working memory in addition to auditory deficits.

Finally, sound stimuli can be more challenging to work with at a technical level than comparable stimuli in the verbal and visual modalities. Sounds do not lend themselves to ‘pencil and paper’ experiments; they are less convenient to administer and more difficult to manipulate than words or pictures. A related issue is that most neuropsychologists are less familiar with the theoretical bases of acoustics, and the practical tools for digital sound synthesis.

Thus, a range of practical problems face current attempts to design auditory assessments suitable for neurological patients. The above discussion suggests that there is no perfect test format; instead, tests will be designed on an individual basis to meet requirements as adequately as possible. In relation to these challenges, a subsidiary aim of this thesis will be to develop assessments

that obviate these problems as far as possible, and thereby facilitate and encourage further neuropsychological work in the auditory modality.

2.3.3 Design of present non-verbal auditory neuropsychology battery

As described, the test design options open to the current battery comprise individual sound categorisation, cross-modal matching, and sequential sound comparison. Individual sound categorisation might offer the best method of auditory assessment since it minimises any demands upon attention or working memory, and furthermore, does not implicate the processing of stimuli in a further modality. However, this method is less suitable for sounds that are not easily verbally labelled or categorised, including auditory properties like timbre. In contrast, cross-modal matching of sounds to either words or pictures is likely to be confounded by prominent language deficits in PPA and/or visual semantic deficits in SD respectively. Additionally, it is likely to be less useful for the assessment of sound properties including timbre for which there are infrequently suitable cross-modal stimuli to which sounds can be matched. Finally, the use of sequential sound comparison carries the disadvantage of requiring subjects to briefly hold sounds in memory, such that results might be confounded by working memory impairments. However, whilst such impairments are found in PNFA (e.g., Grossman et al., 2005), they are less prominent than observed language difficulties, suggesting that sequential sound comparison might be preferable to cross-modal matching. Furthermore, as already suggested, the comparison of sequential sounds is often the only method suitable for measuring sound property discrimination (e.g., timbre discrimination). In view of these factors, sequential comparison was chosen as the format for the majority of tests. However, for two reasons, individual sound categorisation was the most preferable method for constructing a test at the apperceptive level: firstly, constituent sounds were derived from two categories, making them by definition suitable for categorisation; secondly, the use of this method would make the auditory apperceptive test comparable to a canonical test of visual apperception (Object Decision test, Warrington and James, 1991) which is also based on a categorisation procedure (albeit with certain operational differences). Thus, sequential sound comparison was implemented

throughout the perceptual property and semantic tests, whilst individual sound categorisation was used for the assessment of apperceptive processing.

2.4 Background

As described in the introduction (section 1.5), the neuropsychology of non-verbal auditory processing has been relatively little studied and remains poorly understood. However, evidence from corresponding neuroimaging studies of healthy subjects increasingly implicates distributed neural networks in various sub-processes of non-verbal auditory cognition (Wessinger et al., 2001; Leaver and Rauschecker, 2010; Griffiths et al., 2007; Staeren et al., 2009; Peretz et al., 2009; Hyde, Zattorre and Peretz, 2010; Griffiths and Warren, 2002, 2004). At the same time, the degenerative dementias are a group of neurological diseases characterized by the selective anatomical degeneration of functionally coherent neural networks (Sonty et al., 2007; Seeley et al., 2009; Zhou et al, 2010; Buckner et al., 2009; Meslaum, 2009). In particular, two syndromes of primary progressive aphasia (PPA), namely semantic dementia (SD) and progressive non-fluent aphasia (PNFA), are likely from both neuropsychological and anatomical perspectives to cause deficits of non-verbal auditory processing. SD involves the progressive deterioration of semantic knowledge pan-modally (Bozeat et al., 2000; Coccia et al., 2004; Luzzi et al., 2007), in association with anatomical damage to an object recognition network centred upon the anterior temporal lobes (ATLs; Seeley et al., 2009); thus, patients are likely to exhibit semantic processing deficits in the auditory modality (see section 1.5.5). PNFA involves damage to a peri-Sylvian network (Seeley et al., 2009) which overlaps with areas implicated in aspects of non-verbal auditory cognition including property, apperceptive, and semantic stages of processing (Zatorre and Belin, 2001; Altmann et al., 2010; Lewis et al., 2006; Staeren et al., 2009; Leaver and Rauschecker, 2010). Further, behavioural evidence suggests that PNFA may cause deficits during the perceptual analysis of sounds with complex spectrotemporal structures (Jorgens et al., 2008; Otsuki et al., 1998; Iizuka et al., 2007). Therefore, the non-verbal auditory assessment of PNFA and SD, using tests situated at a range of processing levels, may illuminate the impact of network degeneration upon sound cognition and thereby provide insight into corresponding mechanisms in the healthy brain.

2.5 Hypotheses

Hypotheses for the current study, based on the previous literature review (sections 1.5 and 1.6), were as follows: (i) different dementia syndromes show distinct profiles of non-verbal auditory processing impairments; (ii) PNFA leads to predominant deficits of perceptual (property and apperceptive) processing; (iii) SD leads to predominant deficits of semantic processing; (iv) given that PNFA and SD involve damage to functionally coherent and distributed cortical regions, both syndromes may also lead to less prominent deficits at additional processing levels (e.g., semantic in PNFA; perceptual in SD).

2.6 Methods

2.6.1.1 Subjects

Twenty consecutive patients (12 males) who met consensus criteria (Neary et al., 1998) for a diagnosis of PNFA (n = 12) or SD (n = 8) were recruited from a tertiary cognitive disorders clinic. Twelve healthy control subjects with no history of neurological or psychiatric illness also participated. Demographic data for all subjects are summarised in Table 2.1. Patient and control groups were well matched for educational background, and the patient groups were well matched for disease duration. Males were under-represented in the control group relative to the patient sample. The mean age of the patients with SD was younger (Mann Whitney $p<0.01$) than either the PNFA group or the healthy control group. Age and gender were accordingly incorporated as covariates in all subsequent analyses.

Table 2.1 Demographic data by group

	N		Age (years)	Education (years)	Dis. dur. (years)
	Total	**Female**	**Mean (std. dev)**		
PNFA	8	4	73.1 (6.1)	13.4 (2.6)	6.4 (2.5)
SD	12	4	61.5 (4.9)	13.1 (2.3)	6.3 (1.4)
Control	12	8	71.3 (4.9)	12.0 (2.3)	N/A

KEY: Dis. dur., disease duration; PNFA, progressive non-fluent aphasia; SD, semantic dementia; std. dev, standard deviation.

2.6.2 Background assessments

2.6.2.1 Brain image acquisition

Brain MRI scans were acquired in all subjects on a 1.5T GE Signa scanner (General Electric, Milwaukee, WI). T1-weighted volumetric images were obtained using a spoiled fast GRASS sequence technique with a 24-cm field of view and 256 x 256 matrix to provide 124 contiguous 1.5-mm-thick slices in the coronal plane. The scan acquisition parameters were as follows: repetition time = 15 milliseconds; echo time = 5.4 milliseconds; flip angle = 15°; inversion time = 650 milliseconds.

2.6.2.2 Assessment of sub-cortical auditory function

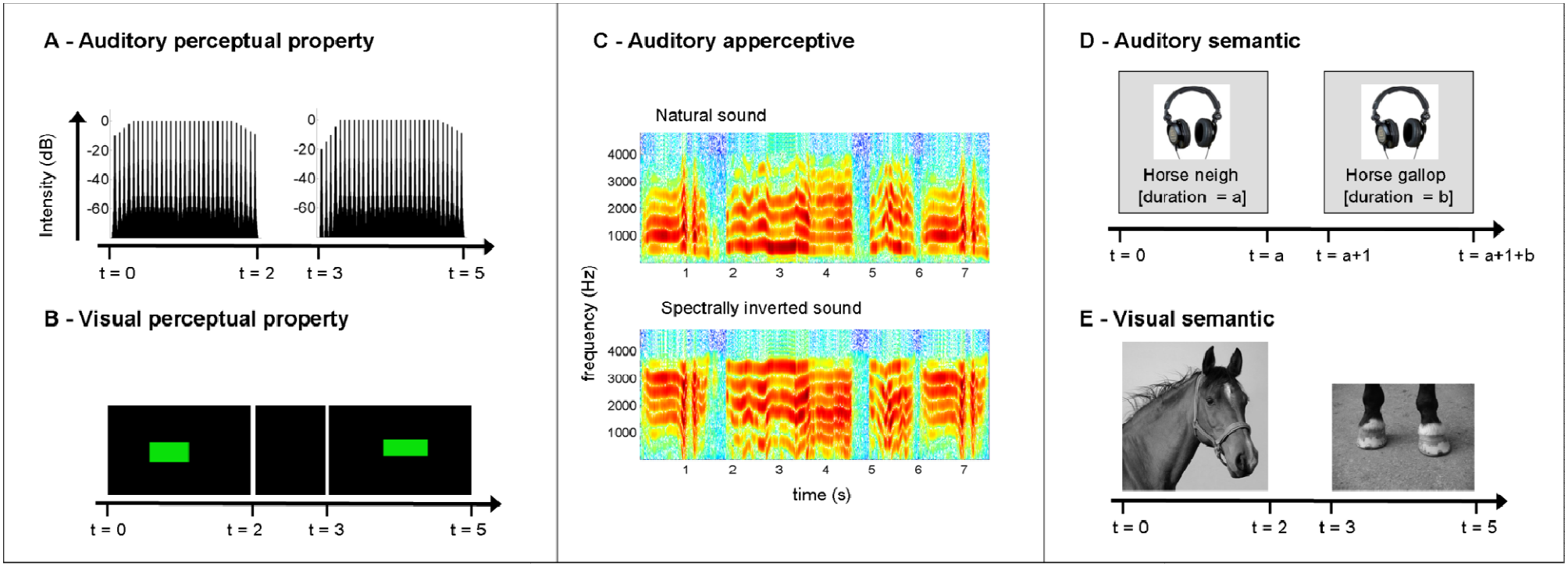
In the majority of patients (14/20), peripheral hearing was assessed using Pure Tone Audiometry (PTA), tympanometry, and transient otoacoustic emissions (OAEs). In the remaining patients and all healthy control subjects a brief PTA screening assessment was used. Auditory Brainstem Responses (ABRs) were also recorded in a subset of patients (10/20). These procedures are summarised in the chapter appendix (section 2.10.1). For each subject, pure tone thresholds at 0.5, 1 and 2 KHz at each ear were averaged to give a '3 Frequency Average' (3FA), and thresholds at 4, 6 and 8 KHz were averaged to give a 'High Frequency Average' (HFA). 3FA and HFA were then compared to age-corrected norms (Davis, 1995) and categorised as normal or abnormal. Lastly, for each subject, categorisations were collapsed across ears to give a single measure for each subject within each hearing range (3FA-S, HFA-S), which was considered abnormal only if both ears were abnormal.

2.6.2.3 General neuropsychological assessment

General neuropsychological functions were assessed in patients using standard measures (summarised in Table 2.3), at the time of initial recruitment and contemporaneous with the experimental assessment. Assessments at the time of initial recruitment provided a neuropsychological characterisation of patient subgroups: these included measures of non-verbal fluid intelligence and executive processing (Raven's matrices: Raven et al., 2003; Trail Making: Reitan, 1959), attention (Dual Number Cancellation: Mohs et al., 1997), object naming (novel test), spoken word repetition (McCarthy and Warrington, 1984),

word comprehension (a shortened 30-item version of the British Picture Vocabulary Scale, BPVS: Dunn et al, 1982), grammar processing (a shortened 20-item version of the Test of Reception of Grammar: Bishop, 1989), reading (novel test of irregular words) and face recognition (Warrington and James, 1967). Contemporaneous tests allowed correlation of general neuropsychological functions with experimental findings: these tests comprised measure of executive function (Non Verbal Design Fluency: Delis et al., 2001), verbal semantic processing (Synonyms test: Warrington et al., 1998), visual (pictorial) recognition memory (Camden Memory Tests: Warrington, 1996), and visual apperceptive processing (Object Decision test: Warrington and James, 1991). All patients completed the Mini-Mental State Examination (MMSE: Folstein et al., 1975), a general cognitive screening instrument, as an index of disease severity at the time of the experimental assessment.

Figure 2.1 Schematic of experimental stimuli and presentation sequences



KEY: A and B: schematics of stimuli from the auditory and visual property perception tests, and the presentation sequence used; C: schematic of spectral inversion of a complex sound, as used in the auditory apperceptive test; D and E, examples of auditory and visual semantic stimulus pairs, and a schematic of the presentation sequence used; t, time (seconds). Sound examples for each test are also provided (numbers 12-15).

2.6.3 Experimental assessment of auditory cognition

2.6.3.1 Overall battery design

A novel neuropsychological battery was designed as a preliminary tool with which to probe property, apperceptive and semantic auditory processing. Additionally, to assess the modality-specificity of any auditory disorders identified, analogous tests in the visual modality were also designed.

2.6.3.2 Property processing

To assess perceptual property processing, a test of spectral shape discrimination was designed. This specific test was chosen for several reasons. Firstly, spectral shape is an important determinant of timbre, and there are several neuropsychological reports of dystimbria associated with underlying deficits for spectral processing (e.g., Griffiths et al., 2007; Kohlmetz et al., 2003; Samson et al., 2002). Secondly, it can be argued that spectral shape discrimination is broadly analogous to visual shape discrimination, such that an examination of these processes in parallel would enable the disambiguation of general from modality-specific effects. Specifically, shape perception in vision requires the integration of information across two (spatial) dimensions. Analogously, since spectral shape is defined as the distribution of energy across different frequencies, it can be argued that spectral shape perception also necessitates the integration of information across two dimensions, i.e. intensity information across multiple frequency bands. Thus, broadly analogous tests of spectral and visual shape processing were designed to facilitate the examination of modality-specific effects within auditory property perception.

2.6.3.2.1 Stimuli

Sounds were digitally generated using a Matlab-based signal-synthesis algorithm (Warren et al., 2005a) enabling the generation of harmonic series with specified spectral shape. Different ‘trapezoidal’ spectral shapes were created in the frequency domain by varying the gradient of the ‘ascending’ slope of the frequency trapezoid (see Figure 2.1 and sound example 12). Frequency bandwidth, sound duration and temporal envelope were held constant. Fundamental frequency and average intensity (Root Mean Square level) value were varied across the stimulus set, to reduce any tendency for subjects to use the absolute intensity level in a particular frequency band to perform the test. 32

sound pairs were created: 16 ‘same’ pairs comprising identical sounds, and 16 ‘different’ pairs comprising sounds that differed only in spectral shape. Sounds in each pair were presented sequentially (inter-stimulus interval 1 second).

As visual analogues of the spectral shape stimuli, rectangles of varying dimensions were generated by holding total flux (area) constant whilst varying the height/length ratio. Rectangles had constant hue and were presented on a uniform black background (see Figure 2.1, section B). 32 rectangle pairs were created (16 same, 16 different). To minimise differences in working memory load between stimulus modalities, rectangles within each pair were presented sequentially with the same inter-stimulus interval as the sound pairs.

2.6.3.2.2 Task

Stimulus pairs were presented in a fixed balanced order: experimental conditions were evenly distributed in a non-predictable fashion throughout the test sequences. For each test, after presentation of each pair, the subject was asked “Are they the same or different?”

2.6.3.3 Apperceptive processing

There already exists a canonical visual test which assesses the integrity of perceptual (structural) object representations: the object decision test (Warrington and James, 1991). As discussed in the literature review (see section 1.5.3.1), such visual perceptual object representations are held to combine information about the features and 3D structure of particular objects, to facilitate their recognition despite physically different viewing conditions; this process is known as object invariance. In audition, analogous perceptual object representations known as auditory templates are postulated (e.g., Griffiths and Warren, 2002) and may provide the cognitive substrate for auditory object invariance (enabling the recognition of sounds under different listening conditions), or a short-cut to auditory object categorisation. Thus, the current auditory apperceptive test was designed to examine the integrity of auditory object templates in an analogous fashion to the original visual object decision test. The visual object decision test requires subjects to categorise 2D black and white silhouettes into ‘real’ and ‘not real’ objects. Therefore, in an analogous fashion, the current auditory object decision test sought to examine the categorisation of real and unreal sounds.

The key experimental manipulation here was spectral inversion, SI (Blesser, 1972). The SI procedure flips the energetic frequencies present in a broadband sound (i.e. exchanges the energy present between higher and lower frequencies) about a user-specified frequency value (see Figure 2.1, section C) to create a frequency structure that is 'impossible' in a natural sound. Example sounds are provided: sound 13 is a natural animal call and sound 14 is the same call after SI. This procedure retains the spectrotemporal complexity of a natural sound but produces a percept of an artificial or 'alien' sound in normal listeners (Scott et al., 2000). While SI animal calls (for example) are highly artificial, the procedure preserves many acoustic features of the original sound, such that SI and natural sounds are not differentiated by spectral content or temporal envelope alone. Rather, SI alters more complex acoustic features, including spectral and spectrotemporal modulations that are likely to be critical for disambiguating natural from synthetic sounds (e.g. Chi et al., 2005).

2.6.3.3.1 Stimuli

20 animal and human vocalisations were selected from online sound databases (e.g., www.sonomic.com; www.soundrangers.co.uk). Individual items were chosen to vary in the ease with which they are identified by normal subjects: this effect was quantified in a second group of healthy age-matched controls who did not participate in the experiment proper (n = 18, 17 females; age: mean = 68.7 years, standard deviation = 6.7; NART IQ: mean = 122.6, standard deviation = 4.5). For each item, subjects were asked (i) "What is it?" and (ii) "How difficult was that to recognise?" (subjects answered using a 6 point Likert scale: 0= didn't recognise, 1=very difficult, 2= difficult, 3=moderate, 4=easy, 5=very easy). Across the set of sounds, responses to question (i) provided an index of frequency of correct identification while responses to question (ii) provided a rating of difficulty of identification for each sound. Further details about this procedure, the complete stimulus list and their corresponding ratings are presented in the chapter appendix, section 2.10.2.1. For the experimental test, each natural sound was modified using a method of SI to create an additional set of 20 novel sounds.

As a visual analogue of this novel auditory apperceptive test, subjects completed an established and standardised test of visual apperception (Object Decision, Warrington and James, 1991) based on discrimination of real from novel 2D silhouettes. The test comprises 20 arrays of 4 silhouettes.

2.6.3.3.2 Task

For the auditory apperceptive test, the 40 sounds (20 non-SI, 20 SI) were presented individually in a fixed balanced order: conditions were randomly distributed throughout the test sequence. For each sound, the subject was asked: “Is it a real thing or not a real thing?” The visual apperceptive test was administered in standard fashion (Warrington and James, 1991): on each trial, the subject was shown the four silhouettes in an array, and asked to point to the real object. Since the auditory test involved just one item per trial, whilst the visual test involved four, response procedures for the two tests were not completely analogous; however, both required the categorisation of a single item using the same binary forced choice options.

2.6.3.4 Semantic processing

Here, assessments were designed to examine the association of conceptual meaning with environmental sound objects, and in an analogous test, with visual (photo) objects.

2.6.3.4.1 Stimuli

Environmental sounds were obtained from online sound databases (e.g. www.sonomic.com; www.soundrangers.co.uk). 32 individual sounds representing a range of human and animal sounds and environmental noises were chosen and arranged to constitute 32 pairs of sequentially-presented sounds (see chapter appendix section 2.10.2.2, Table 2.8). Picture analogues of the sound pairs were obtained using online image search engines and image databases (e.g. http://images.google.co.uk, www.flckr.co.uk). Pictures were 32 visual object parts, chosen such that each object part was easily recognisable as a distinct entity in isolation from the rest of the larger object to which it belongs. The identifiability of the sounds and pictures was assessed using the same procedure as for the stimuli used in the apperceptive test, in the same group of untrained healthy age-matched controls. Both auditory and visual semantic stimuli were highly recognisable: identifiability ratings showed that

although pictures were overall easier to identify than sounds, sounds were nonetheless frequently identified successfully, and moreover, stimulus identification difficulty ratings were similar between the two modalities.

In the experimental test, sounds were paired such that the individual sounds in a pair had dissimilar acoustic characteristics, to reduce the availability of perceptual matching cues. In the 'same' pairs, sounds were produced by the same source (e.g. horse neighing, horse galloping; sound example 15). In the 'different' pairs, sounds were produced by different sources (e.g., horse neighing, human coughing). The test design is presented schematically in Figure 2.1, section D. All 32 sounds appeared once in the 'same' and once in the 'different' condition, to control for item-specific effects. From the set of 32 pictures, 16 'same' and 16 'different' pairs were created such that pictures within a pair had dissimilar visual perceptual characteristics (e.g., see Figure 2.1, section E). All 32 pictures appeared once in the 'same' and once in the 'different' condition. To minimise differences in working memory load between stimulus modalities, pictures within each pair were presented sequentially with the same inter-stimulus interval as the sound pairs. All sound and picture pairs, together with their normative data, are listed in the chapter appendix (section, 2.10.2.2, Table 2.8).

2.6.3.4.2 Task

Stimulus pairs were presented in a fixed balanced order: conditions were randomly presented throughout the test sequence. To reduce any effects from semantic priming between modalities, subjects completed the semantic picture test first, followed by at least one other unrelated test, and then the semantic sound test. On each sound trial, the subject was asked: "Are the sounds made by the same thing or different things?" On each picture trial the subject was asked: "Are the pictures part of the same thing or different things?"

2.6.3.4.3 General testing procedure for assessment of auditory cognition

All experimental auditory neuropsychological tests were run under Matlab 7.3® (www.mathworks.com) on a notebook computer. Subject responses were entered directly by the experimenter, and saved for offline analysis. Sounds

were delivered using a high-fidelity external soundcard (Edirol® UA-4FX) and linear headphones (Sennheiser® HD265) at comfortable listening level (peak absolute sound pressure levels between 70 and 100 dB). Images were presented on a 17" high resolution monitor. For all tests, performance on each test item was probed using a simple question with two alternative responses. Answers could be given verbally, or in the case of speech output difficulty, by pointing to a prompt sheet displaying the two responses. Each test was prefaced with a brief example phase to ensure subjects understood the test.

2.7 Analysis

2.7.1 Group data

Linear regression was used to relate scores for each test (general neuropsychological and experimental) to group membership (PNFA, SD or healthy control). In part due to the small size of the subject groups assessed in this study, data were not normally distributed, with heterogeneous levels of variance between groups, individual subject effects, and (in the control group) a high proportion of ceiling results. These limitations were partly addressed using bootstrapping procedures, which facilitate parametric statistical analyses on non-normally distributed datasets: such procedures estimate statistical parameters based on a large number of random samples (with replacement) from an original dataset. In this study, bootstrapped confidence intervals (95% CIs, bias-corrected, accelerated with 2000 replications) were calculated for all regression coefficients within each linear regression analysis and used to infer statistical significance. Each linear regression model included age and gender as covariates, with the exception of the models for Non Verbal Design Fluency and Trail Making which are internally corrected for age and gender. Additionally, a separate analysis was conducted to evaluate responses to the subset of 'real' (non-SI) sounds in the auditory apperceptive test. Here, a mixed effects logistic regression model was used to relate, for each sound, the probability of a correct response to its corresponding difficulty rating (for details of difficulty ratings, see section 2.10.2.1). This model included fixed effects (sound difficulty rating, group membership and their interaction) and crossed random effects (individual subjects, individual sounds). The model was fitted using a Laplacian approximation. All analyses were carried out using STATA 10™.

In order to assess factors influencing performance on particular components of the experimental auditory battery, patient performance on individual auditory tests was assessed in relation to other tests in the battery, general neuropsychological functions and general measures of disease severity (clinical disease duration, MMSE) using a correlation analysis (Spearman's ρ). This analysis was carried out separately in the PNFA and SD groups, to take into account their different auditory profiles.

2.7.2 Individual data: auditory and visual cost analyses

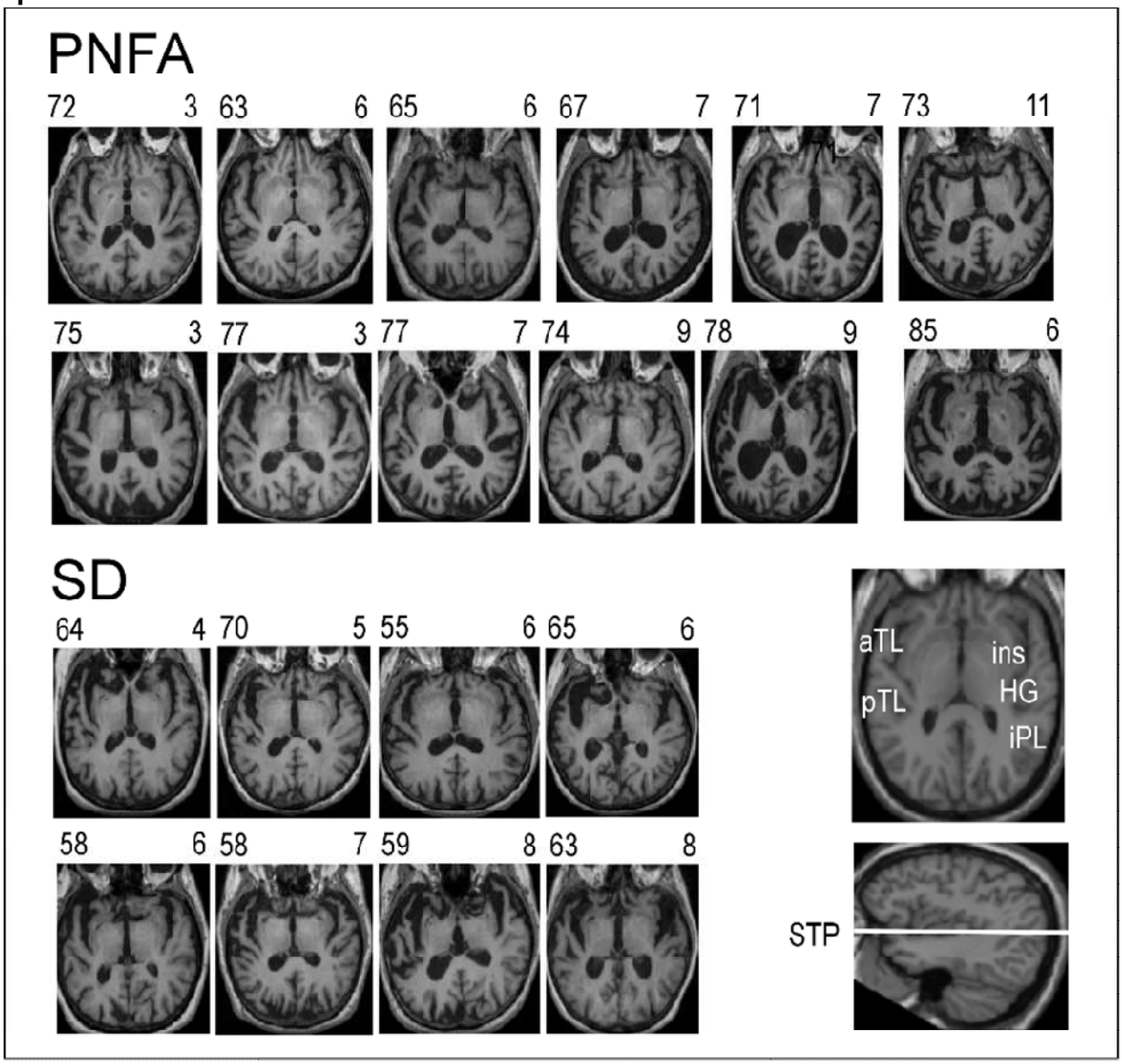
Individual subject performance profiles were examined for modality-specific effects. For both the perceptual and semantic levels of assessment, individual subjects were categorised according to whether their performance showed an 'auditory cost' (performance worse on the auditory than the analogous visual test) or no auditory cost (performance equivalent between modalities or worse in the visual modality). Subjects were also categorised according to whether their performance showed a 'visual cost' at each test level using analogous criteria. Proportions of subjects showing costs were compared between groups using exact logistic regression, adjusting for age and gender.

2.8 Results

2.8.1 Brain imaging

Individual brain MR findings for patients in the PNFA and SD groups are presented in Figure 2.2. Inspection of sections aligned to show key auditory cortical areas in and surrounding the superior temporal plane gives an impression of the range of variation in the distribution and severity of structural damage involving these areas in PNFA and SD. In PNFA, atrophy showed wide variation both in the degree of leftward cerebral asymmetry and, within each hemisphere, the relative involvement of anterior and posterior areas. In contrast, the SD group showed a more uniform atrophy pattern with involvement chiefly of the anterior temporal lobes, initially with predominant involvement of the left temporal lobe and increasingly bi-temporal involvement with increasing disease duration.

Figure 2.2 MR brain sections showing auditory cortices in PNFA and SD patients



Sections of each patient's volumetric T1-weighted MR brain volume are shown. Sections have been tilted to run along the superior temporal plane (STP) to show key auditory cortical areas: the site of primary auditory cortex in Heschl's gyrus (HG), and surrounding non-primary areas in anterior temporal lobe (aTL), posterior superior temporal gyrus and planum temporale (posterior temporal lobe: pTL), insula (ins) and inferior parietal lobe (iPL). For all brain images, the left hemisphere is shown on the left. For reference normal auditory cortical anatomy is shown on the inset sections (lower right) from the brain of a healthy younger individual. Brain images from the progressive non-fluent aphasia (PNFA) group are shown above and the semantic dementia (SD) group below. Above each image is shown the patient's age (left) and clinical disease duration (right) in years at the time of the scan. Within each group brain images have been arranged loosely in order of disease duration; the PNFA group had an older age range and a wider variation in age, and to reflect this, images have been further clustered to show younger patients above and older patients below.

2.8.2 Sub-cortical auditory function

Abnormal PTA profiles were documented in 2/12 patients in the PNFA group (both 3FA; bilateral), 2/8 patients in the SD group (one 3FA, one HFA; bilateral), and one healthy control subject (HFA; bilateral). OAEs were consistent with PTA thresholds for all individuals. Abnormal ABRs were recorded in 4/6 patients (2 bilateral) in the PNFA group and 2/4 patients (none bilateral) in the SD group. PTA and ABR data are summarised in Table 2.2.

Table 2.2 Summary of findings for sub-cortical auditory function

Pure Tone Audiometry (PTA)						
	Total assessed	3FA		HFA		**Total abnormal for age**
		Normal for age	Abnormal for age	Normal for age	Abnormal for age	
PNFA	12	10	2	12	0	**2**
SD	8	7	1	7	1	**2**
Control	12	12	0	11	1	**1**
Auditory Brainstem Responses (ABR)						
	Total assessed	Normal		Abnormal unilateral	Abnormal bilateral	**Total abnormal**
PNFA	6	2		2	2	**4**
SD	4	2		2	0	**2**

KEY: PNFA, progressive non-fluent aphasia; SD, semantic dementia.

2.8.3 General neuropsychological assessment

On baseline assessment of general neuropsychological functions, the PNFA and SD groups had profiles consistent with their clinical diagnoses (Table 2.3): the PNFA group showed impairments chiefly affecting naming, single word repetition, reading, executive function and attention; while the SD group showed more severe impairment of naming with additional deficits of single word comprehension and face recognition but normal single word repetition and executive functions. On contemporaneous general neuropsychological assessment, both groups showed normal performance in the visual Object Decision task but impaired performance on other measures relative to healthy controls (Table 2.3). The PNFA group performed significantly less well than the SD group on Non Verbal Design Fluency, while the SD group performed significantly less well than the PNFA group on the concrete words component of the Synonyms test.

Table 2.3 Results of general neuropsychological assessment: raw scores and differences in group means adjusted for age and gender

Test	Raw scores				Differences in group means		
		Mean (std. dev.)			Mean difference (95% CI)		
	Max score	PNFA (N=12)	SD (N=8, *N=7)	Control (N=40)	PNFA - SD	PNFA - Control	SD – Control
Baseline Neuropsychology							
Nonverbal intelligence	12	5.2 (2.8)	*8.1 (2.7)	7.4 (2.7)	-1.6 (-4.5, 1.5)	-1.8 (-3.7, 0.1)	-0.2 (-2.6, 2.0)
Naming	20	13.8 (5.7)	*4.1 (3.8)	19.4 (1.1)	**10.4 (5.7, 14.0)**	**-5.2 (-8.7, -2.7)**	**-15.7 (-18.1, -12.2)**
Word-picture matching	20	19.3 (1.2)	*12.1 (5.4)	19.9 (0.3)	**7.4 (3.7, 11.1)**	-0.4 (-1.5, 0.1)	**-7.8 (-11.7, -4.2)**
Famous face recognition	12	10.5 (2.2)	*6.4 (5.3)	11.6 (0.7)	**3.8 (0.3, 7.9)**	**-1.2 (-2.7, -0.1)**	**-5.0 (-8.9, -1.6)**
Famous face recall	12	5.9 (3.6)	*1.0 (2.2)	9.6 (1.6)	**4.4 (1.1, 6.8)**	**-3.9 (-6.2, -1.9)**	**-8.3 (-9.6, -5.7)**
Repetition	30	24.5 (9.3)	*30.0 (0.0)	29.9 (0.3)	**-5.1 (-12.1, -1.4)**	**-5.2 (-11.5, -1.4)**	-0.1 (-1.6, 1.3)
Reading	30	19.5 (8.1)	*14.9 (10.7)	27.0 (2.9	5.0 (-4.5, 14.1)	**-7.3 (-12.8, -3.2)**	**-12.4 (-20.2, -4.7)**
Grammar	20	16.1 (2.6)	*15.6 (3.6)	19.4 (0.7)	0.6 (-2.3, 4.1)	**-3.3 (-4.9, -1.8)**	**-3.9 (-6.9, -1.7)**
Dual number cancellation	40	13.4 (5.0)	*22.7 (5.9)	24.9 (5.3)	**-5.7 (-11.0, -0.7)**	**-10.1 (-13.1, -6.5)**	-4.4 (-8.9, 0.2)
Trail Making A (scaled)	-	4.9 (3.4)	*8.4 (3.2)	9.3 (2.2)	**-3.5 (-6.3, -0.4)**	**-4.3 (-6.1, -2.1)**	-0.8 (-3.2, 1.5)
Trail Making B (scaled)	-	4.6 (2.9)	*9.0 (3.4)	10.2 (2.7)	**-4.4 (-7.6, -1.8)**	**-5.6 (-7.5, -3.8)**	-1.2 (-3.3, 1.7)
Contemporaneous Neuropsychology							
MMSE	30	20.9 (6.6)	18.9 (6.8)	-	-0.6 (-9.9, 10.5)	-	-
Object decision	20	17.1 (6.1)	16.5 (3.1)	17.3 (2.5)	0.8 (-1.4, 3.4)	-0.3 (-1.2, 0.7)	-1.1 (-3.7, 1.0)
NVDF (∑ scaled scores)	-	6.4 (1.8)	8.6 (2.5)	12.4 (2.4)	**-2.2 (-4.2, -0.2)**	**-5.9 (-7.2, -4.7)**	**-3.7 (-5.4, -2.0)**
Recog. memory (pictorial)	30	27.4 (3.3)	24.8 (7.4)	29.6 (0.7)	3.1 (-1.1, 9.4)	**-2.0 (-4.2, -0.7)**	**-5.1 (-11.6, -1.1)**
Syn. concrete (2nd er.)	25	10.8 (6.1)	3.9 (3.6)	21.5 (5.3)	**8.7 (4.1, 13.0)**	**-10.1 (-13.5, -5.6)**	**-18.8 (-21.2, -15.2)**
Syn. abstract (2nd er.)	25	9.3 (6.3)	4.4 (7.4)	22.1 (4.8)	4.9 (-3.0, 10.1)	**-13.1 (-16.1, -9.2)**	**-18.0 (-22.2, -11.0)**

Bold numbers indicate significant differences between groups. Controls comprised a previous age- and gender-matched sample. KEY: 2nd er., synonyms scores calculated using the '2nd error procedure' in which raw score was the number of correct items prior to making a 2nd incorrect response; CI, confidence interval; Grammar, shortened Test of Reception of Grammar (TROG); NVDF, Non-verbal Design Fluency; Non-verbal intelligence, shortened Raven's matrices; PNFA, progressive non-fluent aphasia; Recog., recognition; SD, semantic dementia; std. dev, standard deviation; Syn., Synonymns; Word-picture matching, shortened British Picture Vocabulary Scale (BPVS).

2.8.4 Results: Experimental assessment of auditory cognition

Raw behavioural data are shown in Figure 2.3. Bootstrap analyses as described in the analysis section were used to determine the significance of group differences and are presented in Table 2.4. The overall patterns of disease group performance across the set of experimental tests are summarised in Table 2.5.

Table 2.4 Experimental data: differences in group means adjusted for age and gender

	Auditory	**Visual**
	Mean difference (95% CI)	
Perceptual property		
PNFA vs. SD	**-4.2 (-9.1 to -1.1)**	-1.5 (-5.4 to 1.7)
PNFA vs. Control	**-3.4 (-6.5 to -1.4)**	-0.1 (-3.0 to 2.4)
SD vs. Control	0.8 (-1.5 to 3.3)	1.4 (-1.0 to 3.9)
Apperceptive		
PNFA vs. SD	-1.5 (-5.2 to 1.8)	0.9 (-1.8 to 4.5)
PNFA vs. Control	**-5.9 (-9.7 to -3.4)**	-
SD vs. Control	**-4.4 (-7.2 to -2.0)**	-
Semantic		
PNFA vs. SD	0.9 (-3.9 to 5.6)	**3.0 (0.3 to 8.9)**
PNFA vs. Control	**-4.1 (-6.5 to -2.2)**	**-1.4 (-3.0 to -0.5)**
SD vs. Control	**-5.0 (-9.6 to -1.2)**	**-4.4 (-11.1 to -1.7)**

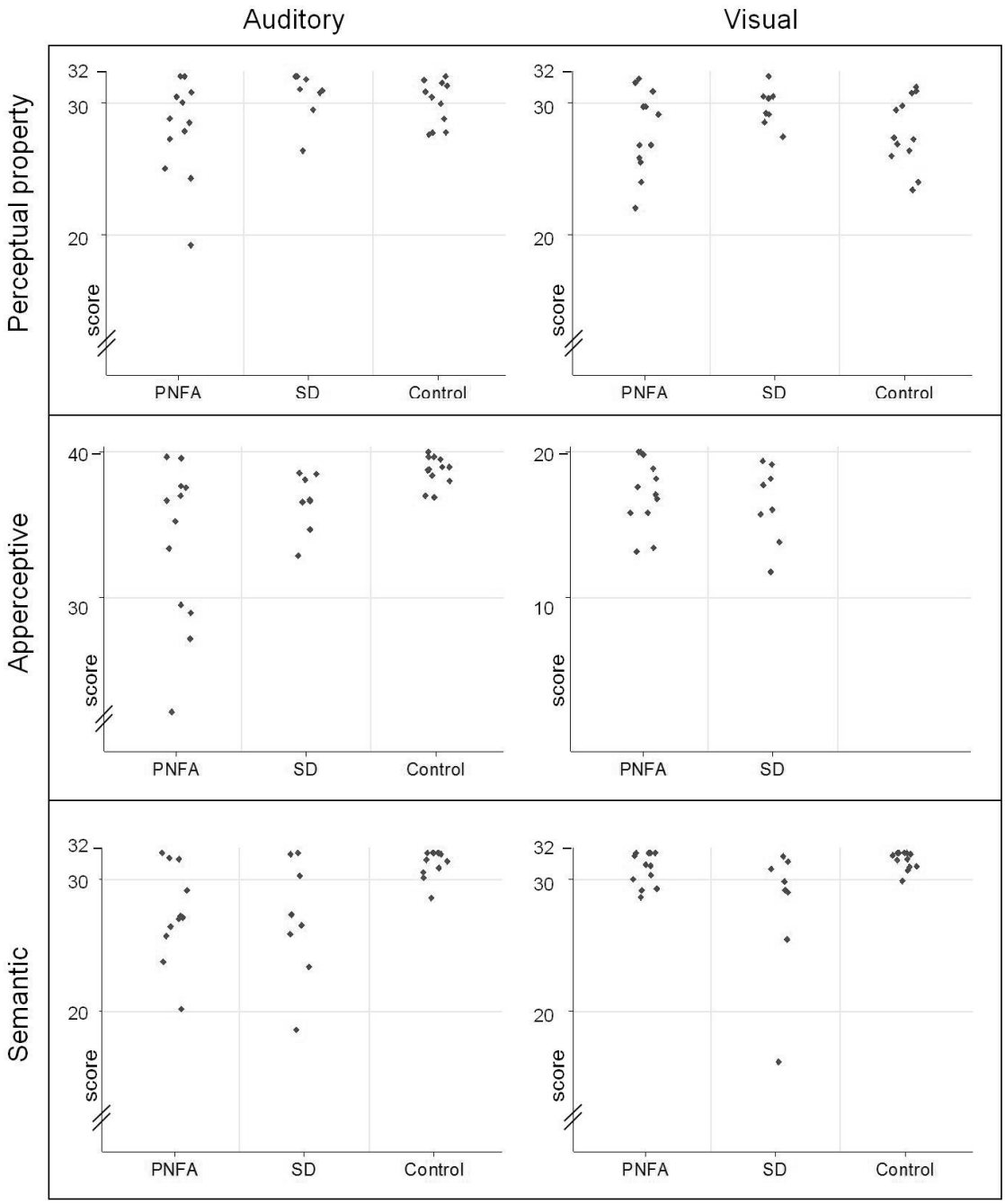
Bold numbers indicate significant differences between groups. KEY: PNFA, progressive non-fluent aphasia; SD, semantic dementia. *Although the visual apperceptive (Object Decision) test aimed to probe similar cognitive processes to the auditory apperceptive test, it is not precisely analogous: see methods section for details.

Table 2.5 Summary of disease group performance patterns on experimental tests

	Disease group			
	PNFA		SD	
Processing level	Auditory	Visual	Auditory	Visual
Perceptual property	++	-	-	-
Apperceptive	+	-	+	-
Semantic	+	+	+	++

KEY: ++, significant deficit compared to alternate patient group and healthy controls; +, significant deficit compared to healthy controls; -, no significant deficit; PNFA, progressive non-fluent aphasia; SD, semantic dementia.

Figure 2.3 Performance on experimental subtests: raw data



KEY: PNFA, progressive non-fluent aphasia; SD, semantic dementia.

2.8.4.1 Property processing

On the auditory property perception test, the PNFA group was significantly more impaired than both the healthy control group and the SD group. The performance of the SD group did not differ significantly from controls. Performance on the test did not differ materially for patients with and without peripheral hearing loss. On the analogous visual test, performance was equivalent between disease groups and did not differ significantly from controls.

2.8.4.2 Apperceptive processing

On the auditory apperceptive test, both the PNFA group and the SD group were impaired relative to healthy controls. The performance of the PNFA group did not differ significantly overall from the SD group. However, inspection of individual data (Figure 3) suggests that there may be a subgroup of patients with PNFA with more marked impairment on this test.

The performance patterns across the three groups were further assessed for any effect of sound recognition difficulty (identifiability) within the subset of 'real' (non-SI) stimuli. Sound identifiability was significantly associated with performance in the healthy control group: a one unit reduction in the recognition difficulty of a sound was associated with a 110% increase in the odds of correctly stating that the sound was real (95% CI: 6 to 316%, p=0.03). A similar magnitude of association was seen in the PNFA group (75% odds increase per unit difficulty reduction; 95% CI: 8 to 183%, p=0.02), but not in the SD group (9% odds increase per unit difficulty reduction; 95% CI: -52 to 144%, p=0.8). Despite the variation in the significance of this association across the three groups (significant in the control and PNFA groups; non-significant in the SD group), a global test for a difference of the association between groups was not statistically significant, reflecting the wide confidence intervals within each group.

On the standardized visual apperceptive (Object Decision) test, regression analysis did not show significant differences in mean performance between each of the disease groups and healthy controls, or between the disease groups. 1/12 patients with PNFA and 1/8 patients with SD scored below the 5th percentile of published age control norms (Warrington and James, 1991).

Although this visual test and the experimental auditory apperceptive test were not directly comparable, it is noteworthy that on the corresponding auditory test 7/12 patients with PNFA and 5/8 patients with SD scored below the range of the healthy control sample. These findings would be in keeping with a more severe impairment of apperceptive processing within the auditory than the visual modality.

2.8.4.3 Semantic processing

On the auditory semantic test, the PNFA group and the SD group were comparably impaired relative to healthy controls. The performance of the PNFA group did not differ significantly from the SD group. On the visual semantic test, both disease groups were impaired with respect to the control group, however performance of the SD group was significantly worse than the PNFA group.

2.8.4.4 Correlation analyses

In the PNFA group, performance on both the auditory perceptual tests and the auditory semantic test was positively associated (both ρ 0.60*;* $p<0.05$) with performance on the auditory apperceptive test. Additionally, performance on the auditory apperceptive task was positively associated (ρ 0.70; $p<0.05$) with performance on the visual object decision task. However, experimental test performance was not significantly associated with other contemporaneous general neuropsychological or disease severity measures in the PNFA group. In the SD group (but not the PNFA group), performance on the auditory semantic task was strongly positively associated (ρ 0.97; $p<0.001$) with performance on the visual semantic task, with some evidence of a positive association with performance on the Synonyms test (ρ 0.65; $p=0.08$). Additionally, performance on the auditory semantic task was associated with general measures of disease severity (disease duration, ρ -0.97, $p<0.001$; MMSE score, ρ 0.89, $p<0.001$), but was not significantly associated with auditory apperceptive performance. In neither the PNFA nor the SD group was performance on any experimental auditory task significantly associated with a contemporaneous measure of executive function (Non-verbal Design Fluency).

Table 2.6 Auditory and visual cost data

	Auditory cost (AC)		Visual cost (VC)	
	PERCEPTUAL PROPERTY (frequency table)			
	No AC	AC	No VC	VC
PNFA	5	7	7	5
SD	7	1	2	6
Control	11	1	3	9
	Exact Logistic Regression (p value)			
PNFA vs. SD	**0.02**		0.09	
PNFA vs. Control	**0.01**		0.07	
SD vs. Control	1		0.9	
	SEMANTIC (frequency table)			
	No AC	AC	No VC	VC
PNFA	2	10	11	1
SD	4	4	4	4
Control	7	5	8	4
	Exact Logistic Regression (p value)			
PNFA vs. SD	1		0.19	
PNFA vs. Control	0.16		0.25	
SD vs. Control	0.47		0.84	

'Cost' is defined as worse performance in the modality of interest (auditory or visual) than in the alternate modality; see text. Frequency tables show numbers of subjects with and without cost for the modality of interest by group and test level (perceptual property or semantic). Corresponding p values are from exact logistic regression models relating cost to group membership, adjusting for age and gender; bold numbers indicate significant differences between groups. **KEY:** PNFA, progressive non-fluent aphasia; SD, semantic dementia.

2.8.4.5 Individual data: auditory and visual cost

There was evidence ($p<0.05$) that patients with PNFA were more likely than patients with SD to exhibit an auditory cost on the perceptual property tests, but not on the semantic tests (Table 2.6). Examining individual data, on the perceptual property tests, 7/12 patients with PNFA showed an auditory cost, compared with 1/8 patients with SD; and on the semantic tests, 10/12 patients with PNFA showed an auditory cost, compared with 4/8 patients with SD. There was also borderline statistically significant evidence ($0.05<p<0.1$) that individuals with PNFA were less likely to exhibit a visual cost on the perceptual property tests than each of the other groups.

2.9 Discussion

2.9.1 Syndrome-specific profiles of non-verbal auditory processing impairment

The findings of this study support the existence of specific and distinct disorders of non-verbal auditory processing in two subtypes of PPA, PNFA and SD. Firstly, deficits of property processing were more common in PNFA. Secondly, deficits of apperceptive processing occurred in both PNFA and SD, but the two groups showed different performance profiles indicating damage to distinct underlying processes. Thirdly, deficits of semantic processing occurred in both groups, but biased towards the auditory modality in PNFA and affecting both visual and auditory modalities in SD. Furthermore, an analysis of individual data revealed more severe impairment in the auditory than the visual modality in the PNFA but not the SD group, particularly for property processing. Subsidiary analyses suggested that the observed group-specific effects were not attributable to sub-cortical auditory dysfunction or disease duration. Additionally, the experimental design ensured that findings were not associated with the effects of certain factors that might potentially confound auditory assessment in PPA, such as cross-modal response procedures. While it is likely that the experimental tests engaged other cognitive operations (for example, non-verbal working memory, attention) in addition to auditory processing, a correlation analysis suggested that group-specific effects were not attributable to such generic deficits.

2.9.2 Syndrome-specific profiles: implications for the organisation of non-verbal auditory cognition

As already described, the PNFA group exhibited simultaneous and correlated deficits of property (spectral shape), apperceptive and semantic processing. On the basis of these data alone it is not possible to establish whether this overall performance profile reflects multiple independent deficits, or a primary disorder that gives rise to impairments at related cognitive stages. However, a comparison between this performance profile and that of the SD group may help to characterise the nature of auditory deficits in PNFA. Previous evidence suggests that SD involves a pan-modal semantic processing impairment (e.g., Bozeat et al., 2000), and in line with this idea, the current SD group showed equivalent deficits in the visual and auditory semantic tests, but normal

performance during auditory property perception. In contrast, the PNFA group showed impaired auditory but intact visual semantic processing, alongside impaired auditory property perception. This disease group comparison might suggest that the deficits in PNFA reflect a core impairment of auditory property perception, which also impedes subsequent stages of auditory cognition. Indeed, a range of previous literature suggests that auditory cognition involves the serial flow of information between increasingly complex stages of processing (Rauschecker et al., 1998; Wessinger et al., 2001; Griffiths and Warren, 2004; Binder et al., 2000). Therefore, apperceptive and semantic impairments observed in PNFA might be caused by the cascading effects of a primary perceptual property processing disorder; further, this suggestion gains particular support from the observed correlations between performance in the three stages of processing examined. Thus, these data may indicate a predominant deficit of property perception in PNFA, and thereby, the relative cognitive independence of corresponding processes in the healthy brain. Notably, these conclusions align with previous neuropsychological evidence for selective timbre processing deficits that are likely to involve, to some extent, specific difficulties of spectral analysis (Mazzucchi et al., 1982; Griffiths et al., 2007; Kohlmetz et al., 2003). Additionally, the cognitive independence of spectral processing is indicated by neuroimaging studies that demonstrate regionally circumscribed activity in particular areas of the auditory cortices during relevant tasks (Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010). However, the current association between performances in the different tests is also suggestive of interactions between property, apperceptive and semantic non-verbal auditory deficits in PNFA. This particular notion is strengthened by previous observations that this syndrome involves damage to a functionally coherent peri-Sylvian network (Seeley et al., 2009) which overlaps with areas implicated in diverse non-verbal auditory processes (Zatorre and Belin, 2001; Altmann et al., 2010; Lewis et al., 2006; Staeren et al., 2009; Leaver and Rauschecker, 2010). Additionally, interdependencies between various stages of non-verbal auditory processing are supported by a range of previous studies: neuroimaging results suggest that semantic processing is at least partly contingent on perceptual mechanisms (see section 1.5.5.6.2; Staeren et al., 2009; Leaver and Rauschecker, 2010), and the neuropsychological literature indicates that disorders of sound recognition are

rarely selective, and tend to occur alongside parallel perceptual deficits (see section 1.5.5.4; Clarke et al., 1996). Taken together, the present evidence thereby favours a primary property processing deficit in PNFA that leads to secondary apperceptive and semantic impairments. However, current findings do not rule out the additional presence of independent apperceptive and semantic impairments. For example, the PNFA group's sub-normal performance in both semantic tests (albeit with better performance than the SD group in the visual modality) might suggest the additional presence of a modality-general semantic deficit. Further, if auditory processing networks involve reciprocal as well as serial connections between stages (Griffiths and Warren, 2004; Hackett et al., 1998; Eliades and Wang, 2008; Lee and Winer, 2008; Tourville et al., 2008), such additional deficits might exert a top-down influence upon perceptual property processing, further impairing performance levels. In summary, results tentatively suggest that PNFA involves a predominant impairment of non-verbal auditory property processing affecting the representation of spectral information, and that additional apperceptive and semantic deficits may result from either the bottom-up influence of this disorder, or separate deficits. Whichever interpretation is preferred, the observed correlation between performances in the different tests, together with the derivation of this data from a patient group which typically exhibits atrophy within functionally coherent regions (Seeley et al., 2009), suggests that non-verbal auditory processing may be mediated by a distributed and reciprocally connected network, which shows varying degrees of functional specialisation. Finally, the inspection of the raw data (Figure 3) suggests variable performance within the PNFA group, which might indicate the presence of a sub-set of distinct auditory syndromes perhaps involving varying levels of impairment at each processing stage. Additionally, PNFA is commonly associated with working memory deficits (Grossman et al., 2005), which might in principle interact with mechanisms of auditory processing; thus, future studies are required to determine the level of independence between impairments of non-verbal auditory processing and working memory in this degenerative syndrome.

In SD, auditory deficits were restricted to the apperceptive and semantic tests. Here, impairments were most severe during semantic processing, with correlated performances across the auditory and visual modalities. As before,

current results do not enable specification of the cognitive locus of impairments, which might reflect either multiple independent deficits or a primary disorder that gives rise to secondary deficits. However, a substantial body of previous research in SD strongly indicates a core and pan-modal semantic processing disorder (Mayberry et al,. 2010; Hodges and Patterson, 1996; Bozeat et al., 2000). From this perspective, current observations are likely to reflect a primary semantic deficit, thus providing support for the relative cognitive independence of corresponding mechanisms in the healthy brain; additionally, current findings also support the view that these semantic mechanisms are pan-modal and therefore not specific to the auditory modality. It may be suggested that simultaneous impairments observed here in the SD group at further processing levels might result from this primary semantic disorder. In particular, current apperceptive impairments might be accounted for by disordered top-down input from semantic representations. Although this conclusion is tentative given the absence of any correlation between the relevant tests, it indicates the potential for close connections between auditory semantic and apperceptive processes in the healthy brain. This particular suggestion gains support from previous evidence that SD involves damage to a functionally coherent but anatomically distributed temporo-parietal network (Seeley et al., 2009). Additionally, it aligns with previous studies showing reciprocal neural connections within animal auditory cortices (Hackett et al., 1998; Eliades and Wang, 2008; Lee and Winer, 2008; Tourville et al., 2008), and overlapping apperceptive and semantic substrates in the healthy human brain (Staeren et al., 2009; Leaver and Rauschecker, 2010). In summary, present data may indicate that SD involves a primary pan-modal semantic impairment, which also causes secondary auditory apperceptive impairments via top-down neural connections within a distributed and reciprocally connected non-verbal auditory processing network.

A detailed analysis of patient performance on the apperceptive test lends further support to the above suggested auditory deficits profiles of PNFA and SD. Both groups showed similar levels of impairment on this test overall; however, only the PNFA group exhibited sensitivity to a stimulus difficulty or ‘identifiability’ factor. It can be suggested that this factor predominantly reflected the ease with which the perceptual structures of sounds included in the test were processed: for example, the several different cat calls used here attained varying

identifiability ratings despite belonging to the same narrow semantic category, indicating the influence of their varying spectrotemporal characteristics. Therefore, it can be proposed that the PNFA group's poor performance on this test reflected a perceptual deficit that was somewhat alleviated for sounds with simpler perceptual structures. This conclusion supports the view that this syndrome involves a core property processing deficit, although it might equally indicate a separate apperceptive impairment (i.e., for processing the perceptual structure of whole objects rather than simpler auditory properties); further work will be required to discriminate between these possibilities. By contrast, the absence of a sound identifiability effect in patients with SD indicated that poor performance was not due to a perceptual deficit, and was therefore more likely to reflect the top-down effects of semantic impairment. These findings therefore provide further support in SD for both a core semantic deficit, and the presence of secondary apperceptive deficits which may reflect close interactions between these processing stages. Finally, in this context, the observation of equivalent apperceptive impairments in the PNFA and SD groups lends further support to the notion that non-verbal auditory processing may rely upon reciprocally connected apperceptive and semantic mechanisms instantiated in a distributed neural network.

2.9.3 Associations between behaviour and anatomy

Visual inspection of the individual profiles of atrophy in PNFA and SD patients (Figure 2) suggests group-specific patterns of damage which may provide an anatomical basis for observed auditory performances. The profiles observed – variable peri-Sylvian atrophy in PNFA and more focal, uniform, and leftward-asymmetric anterior temporal lobe atrophy in SD – are consistent with previous anatomical evidence in these PPA syndromes (Gorno-Tempini et al., 2004; Schroeter et al., 2007; Rohrer et al., 2009; Rohrer et al., 2010b; Seeley et al., 2009). Based on evidence from normal subjects (Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010; Warren et al., 2005b; Zaehle et al., 2008), the more marked involvement of posterior peri-Sylvian cortices in the PNFA group would predict auditory perceptual deficits, thus supporting the presence of a core property processing disorder. It is also clear that patients with PNFA have involvement of more anterior peri-Sylvian and inferior parietal areas that might potentially contribute to separate auditory apperceptive and

semantic deficits (Engelien et al., 1995, 2006; Lewis et al., 2004, 2005, 2009; Thierry and Price, 2006). Additionally, the variation in the extent of posterior damage observed in PNFA patients might explain their wide range of behavioural performance (Figure 3) and provide support for the existence of a range of auditory sub-syndromes within this group. In contrast, the more stereotypical involvement of the anterior temporal lobes in the SD group suggests a substrate for the predominant semantic deficits exhibited by these patients. However, anatomical data provided within this study are limited, and all proposed associations between function and anatomy will require further quantitative cross-sectional and longitudinal analyses in larger PPA cohorts.

2.9.4 Discussion summary

Present findings are suggestive of distinct auditory deficits in PNFA and SD, and align with previous knowledge about the cognitive and anatomical phenotypes of these degenerative syndromes. Specifically, PNFA is associated with predominant auditory perceptual processing deficits in association with damage to a posterior peri-Sylvian network; in contrast, SD is associated with predominant semantic deficits in association with damage to an anteriorly-directed temporal lobe network. Findings therefore support the relative cognitive and anatomical independence of perceptual and semantic mechanisms implicated in non-verbal auditory processing. However, further analyses in both groups suggest that associations between property processing, apperceptive and semantic deficits occur in the context of damage to functionally coherent and wide-spread networks; data thus support the notion that non-verbal auditory processing is conducted within distributed and reciprocally connected cortical networks traversing the superior temporal lobes.

2.10 Chapter appendix

2.10.1 Assessment of sub-cortical auditory function

PTA was carried out using a GSI 61 audiometer (Cardinal Health, Hong Kong) with earphones in a sound-treated room. Air-conduction thresholds were measured for each ear at 0.5, 1, 2, 4, 6 and 8 kHz following the procedure recommended by the British Society of Audiology (1981). Results were averaged to facilitate analysis. For each subject at each ear, pure tone thresholds at 0.5, 1 and 2 KHz were averaged to give a '3 Frequency Average' (3FA), and thresholds at 4, 6 and 8 KHz were averaged to give a 'High Frequency Average' (HFA). The 3FA and HFA averages were then compared to age-corrected norms (Medical Research Council National Study of Hearing, Davis, 1995) and categorised as normal (if they fell within the mean+/- 2 standard deviations for that age group) or abnormal. Tympanometry was obtained with a continuous probe-signal 226-Hz tone at 85 dB sound pressure level using a GSI 33 Middle Ear Analyzer (Grason-Stadler Inc, Milford, New Hampshire). Tympanometry results were considered normal if middle ear pressure was -150 mm H2O or greater and compliance was greater than 0.3 cm3. Transient evoked OAEs were measured in both ears using the ILO88/92 Otodynamic Analyzer (Otodynamics, Hatfield, England), with a standard default setup (Kemp et al., 1990). OAE results were classified as normal on the basis of an overall response amplitude signal-to-noise ratio of at least 6 dB and waveform reproducibility of greater than 70%. Subjects were categorised as normal if no deficits at either ear were detected, and abnormal otherwise. ABRs were recorded with the Nicolet Spirit 4 channel equipment (Nicolet, Madison, Wisconsin). Electrodes were placed on the forehead (A) and on each mastoid (A1 and A2); the A electrode was used as the ground. Monaural alternating click stimuli of 100 microseconds were presented at a rate of 11.1/second via headphones. Electrode impedance was less than 5 kOhms. The electrical activity was amplified and filtered (range, 100-3000 Hz). A total of 1000 stimuli were given, with a mean window of 10 milliseconds. A standard minimum intensity of 90 dB was used, provided that clear waveforms with waves I, III, and V were observed; 100 dBnHL was used in those with hearing loss. ABR analysis was restricted to waves I, III, and V. Waveform morphology, peak latency, and interwave latency were compared with normative departmental

data. Again, subjects were categorised as normal if no deficits at either ear were detected, and abnormal otherwise. A small proportion of patients (6/20) and all control subjects had a brief PTA screening test instead of the above procedures (AUDIO-CD™, Digital Recordings). This was performed in a quiet room using pure tones played through a notebook computer and headphones (Sennheiser® HD265). Hearing thresholds were measured for each ear at 1kH (3FA) and 6kH (HFA).

2.10.2 Normative data

2.10.2.1 Auditory apperceptive test stimuli

Stimulus identifiability and difficulty ratings for the subset of 'real' (Non-SI) sounds used in the auditory apperceptive test were obtained in a separate group of healthy control subjects. Subjects were asked to identify each sound (free response) and to rate the sound according to how difficult it was to identify (rather than how difficult it was to name). To make a correct identification, subjects could provide either the precise name or another name from a list of acceptable responses (see Table 2.7). Not all sounds were identified correctly by all subjects prior to the rating of difficulty; in instances where an item was identified incorrectly, the corresponding difficulty rating was not used in the subsequent analysis. To determine the validity of this elimination procedure, the within-subject relation between proportion of correct identifications and mean difficulty rating of all sounds (correctly or incorrectly identified) was assessed across the group and shown to be non-significant (Spearman's rho=0.3, p=0.2). Thus, the difficulty ratings retained in the post elimination analysis were unbiased: controls that identified more sounds correctly (and were therefore over-represented) were not more likely to give higher ratings. For each sound, the mean of all difficulty ratings retained here was used as the overall difficulty rating in subsequent experimental analysis. Details of ratings pertaining to individual stimuli are given in Table 2.7.

Table 2.7 Apperceptive test stimuli and corresponding norms

Name	Acceptable identification responses*	Frequency of correct identifications	Mean stimulus difficulty
human baby cry	baby, child	18/18	5.0
human female sing	person, woman, singer	18/18	4.9
human male yawn	person, man, yawn	18/18	4.9
human male sneeze	person, man, sneeze	18/18	4.9
human baby gurgle	baby, child	18/18	4.8
ram	ram, sheep, goat, lamb	18/18	4.7
lamb	ram, sheep, goat, lamb	18/18	4.6
pig squeal	pig	8/18	4.5
tawny owl	bird, owl	18/18	4.4
elephant	elephant	11/14	4.3
burmese cat	cat, kitten	12/18	3.8
mule	mule, donkey	9/18	3.8
domestic cat	cat, kitten	10/17	3.5
chimpanzee scream	monkey, chimpanzee, ape	4/18	3.5
crane	bird, any bird species	12/18	3.5
sheep	ram, sheep, goat, lamb	4/18	3.5
human female scream	person, woman, child, scream	13/16	3.5
panther	cat, any cat species	2/14	2.0
siamese cat	cat, kitten	2/18	1.5
black bear	bear, any bear species	0/18	-

KEY: * For each sound, the criteria for a correct identification were a response including 1 or more of the listed words, or equivalent synonyms.

2.10.2.2 Semantic test stimuli

Identifiability and difficulty ratings for all stimuli used in the semantic tests were obtained using the same procedures and subjects as for the apperceptive test stimuli. To make a correct identification, subjects were required to provide a name which clearly indicated correct recognition of the object from which the relevant sound or picture pair was made; correct names of whole objects, their defining parts, or synonyms of these names were all acceptable. All subjects identified all pictures correctly, whilst for each individual sound the proportion of subjects providing correct identifications ranged from 72.2% to 100%, mean 95.9% (standard deviation = 6.2%). This discrepancy between visual and auditory identification responses was significant, indicating that the pictures were easier to identify than the sounds (Mann Whitney $z=4.2$, $p<0.01$), although the sounds were nonetheless identified with relative success (see Table 2.8 for

details of individual stimuli). An analysis of stimulus difficulty ratings for all items that were identified correctly (using the same methods as described above) showed that visual and auditory stimulus difficulty also differed (Mann Whitney $z=3.8$, $p<0.01$). However, inspection of mean difficulty ratings for individual stimuli (Table 2.8) shows that this effect was driven by a small subset of the sound stimuli, and that in general, there was little discrepancy between the two modalities.

Table 2.8 Semantic test stimuli pairs and corresponding norms

Visual semantic stimuli								
	'Same' pairs						'Different' pairs	
	1st picture			2nd picture			1st picture	2nd picture
		Norms			Norms			
Object	Name	Freq. of correct identif.	Mean stim. diff.	Name	Freq. of correct identif.	Mean stim. diff.	Name	Name
fish	fish head	18/18	5.0	fish tail	18/18	5.0	fish head	human palm
parrot	parrot head	18/18	4.8	parrot feather	18/18	5.0	parrot head	human toes
cow	cow head	18/18	4.9	cow hide	18/18	5.0	cow head	human foot-sole
person	human ear	18/18	4.9	human foot-sole	18/18	5.0	human ear	cow hide
person	human hair	18/18	4.9	human palm	18/18	5.0	human hair	fish tail
person	human nose	18/18	5.0	human toes	18/18	4.9	human nose	parrot feather
door	door without handle	18/18	4.9	door handle	18/18	5.0	door without handle	tap
sink	sink without tap	18/18	4.9	tap	18/18	5.0	sink without tap	door knob
horse	horse head	18/18	4.9	horse foot with shoe	18/18	4.5	duck head	car tyre
duck	duck head	18/18	4.8	duck webbed feet	18/18	4.8	bike saddle	horse foot with shoe
person	human elbow	18/18	4.9	human teeth	18/18	5.0	car door and body	duck webbed feet
person	human eye	18/18	5.0	human finger	18/18	5.0	horse head	tree branches
tree	leaf	18/18	5.0	tree branches	18/18	5.0	human elbow	light bulb
bike	bike saddle	18/18	4.9	bike wheel	18/18	5.0	human eye	bike wheel
car	car door and body	18/18	4.9	car tyre	18/18	5.0	lamp shade	human teeth
lamp	lamp shade	18/18	4.9	light bulb	18/18	5.0	leaf	human finger

Auditory semantic stimuli								
	'Same' pairs						'Different' pairs	
	1st sound			2nd sound			1st sound	2nd sound
		Norms			Norms			
Object	Name	Freq. of correct identif.	Mean stim. diff.	Name	Freq. of correct identif.	Mean stim. diff.	Name	Name
cat	cat howl	17/18	4.3	cat mew	17/18	4.6	cat howl	human male snore
bird	tawny owl	18/18	4.4	bird flap wings	16/18	3.4	tawny owl	human male sneeze
horse	horse neigh	17/18	4.8	horse gallop	17/18	4.9	horse neigh	human female cough
person	human male whistle	16/17	5.0	human male sneeze	18/18	4.9	human male hum	cat mew
person	human female sing	18/18	4.9	human female cough	18/18	5.0	human female sing	horse gallop
person	human male hum	18/18	4.9	human male snore	18/18	5.0	human male whistle	bird flap wings
phone	telephone	18/18	5.0	dialtone	17/18	4.7	telephone	door creak open
door	door shut	18/18	4.7	door creak open	18/18	4.8	door shut	dialtone
dog	dog bark	18/18	5.0	dog pant	11/13	4.3	rooster cry	train engine (steam)
rooster	rooster cry	18/18	5.0	rooster clucking	18/18	4.6	coins jangle	dog pant
person	human male breaths	18/18	4.3	human male yawn	18/18	4.9	tap dripping in sink	rooster clucking
person	human male laugh	18/18	5.0	human male sigh	18/18	4.7	dog bark	coin dropped
coin	coins jangle	14/16	4.1	coin drops	14/16	4.9	human male laugh	car start
car	car horn	18/18	5.0	car start	17/18	4.6	human male breaths	tap running in sink
tap	tap dripping in sink	17/18	4.6	tap running in sink	18/18	4.7	train horn	human male yawn
train	train horn	13/18	4.4	train engine	17/18	4.5	car horn	human male sigh

KEY: Freq. of correct identif., Frequency of correct identification; Mean stim. diff, Mean stimulus difficulty.

3 Non-verbal auditory object processing in dementia: study 2

3.1 Summary

This chapter comprises a systematic study of non-verbal sound processing in four dementia groups (typical Alzheimer's disease, AD, N=21; progressive non-fluent aphasia, PNFA, N=5; logopenic progressive aphasia, LPA, n=7; progressive aphasia in association with a progranulin gene mutation, GAA; N=1), and in healthy age-matched controls (N=20). A more extensive neuropsychological battery was developed following the results of the previous chapter, including novel tests of property, apperceptive, and semantic processing. All patients had assessments of peripheral hearing and general neuropsychological functions in addition to the experimental auditory battery. Results consolidate and extend the findings of the previous chapter, indicating that dementia syndromes are associated with distinctive profiles of non-verbal auditory processing impairment: PNFA and AD patients exhibited relatively selective property processing and apperceptive deficits respectively. Additionally, the patient with GAA showed substantial preservation of auditory function, but a mild deficit of pitch direction processing and a more severe deficit of auditory apperception. The observation of these relatively selective deficits may indicate the relative independence of corresponding processes in the healthy brain. In contrast, patients with LPA had a generalised auditory deficit that was influenced by working memory function; such data may suggest the presence of close interdependencies between mechanisms of non-verbal auditory cognition and working memory in the healthy brain. Additionally, predominant property and apperceptive processing deficits in PNFA and AD respectively were accompanied by more subtle deficits at further processing stages; this evidence, derived from the examination of dementia patients who typically exhibit damage to functionally coherent neural networks (Sonty et al., 2007; Buckner et al., 2009; Meslaum, 2009; Seeley et al., 2009; Zhou et al, 2010), suggests that non-verbal auditory processing may be mediated by distributed and reciprocally connected networks.

3.2 Aims of the investigation

The present study aimed to develop a second battery that would build upon and extend the findings of the previous chapter. Specific aims were threefold: to develop a battery suitable for the assessment of patients with working memory deficits; to include tests to examine a greater number of perceptual property processing stages; and to use the battery to assess a greater number of dementia syndromes.

3.2.1 To assess patients with working memory deficits

Working memory is a capacity-limited cognitive system for the temporary storage and manipulation of sensory information (Baddeley, 2000). It incorporates two major sub-processes: the passive encoding of sensory information as memory traces which rapidly decay in the space of a few seconds, and the active maintenance (rehearsal) of this information so that it may be held in a temporary store for longer periods of time. Crucially, this latter process of active maintenance allows the manipulation and integration of multiple pieces of information across space and time, thus enabling the creation of new cognitive representations which might facilitate problem solving (Baddeley, 2000). Whilst theories of working memory are predominantly based upon studies using verbal auditory and visuo-spatial stimuli, further research suggests that mechanisms are likely to overlap with analogous processes in the non-verbal auditory modality (e.g., Rama and Courtney, 2005; Protzner and McIntosh, 2007; Protzner, et al., 2009).

Non-verbal sounds generally evolve over time, and working memory may therefore be necessary to track the temporal changes (modulations) occurring across their duration. The importance of such processes will vary for different categories of sounds (compare, for example, the temporal modulations in the sounds generated by waves and a stapler); however, it is likely that all sounds impose a working memory load to some extent. In particular, the tests of the previous chapter were likely to make demands upon working memory processes given requirements to compare sequentially presented sound pairs. However, the dementia syndromes included in this thesis are often associated with working memory impairments (e.g. Rochon et al., 2000; Grossman et al., 2005, Gorno-Tempini et al., 2008), which might therefore influence processes of

non-verbal auditory cognition. In the previous chapter, cognitive processes that may share resources with working memory (e.g., general executive function) were not associated with auditory performance; however, a specific confound of working memory was not ruled out. Patients with the dementia syndrome of logopenic (phonological) aphasia (LPA) suffer particularly prominent deficits of working memory (primarily assessed for speech sounds: Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2008; Rohrer et al., 2010c), and were therefore not included in the previous study. However, LPA involves relatively greater levels of temporal-parietal damage than other primary progressive aphasia (PPA) syndromes (Gorno-Tempini et al, 2004; Rohrer et al., 2010b), and may therefore lead to a unique profile of auditory deficits including predominant apperceptive impairments (see section 1.6.3). In view of these factors, the present study aimed to develop a second neuropsychological battery involving minimal working memory requirements. Additionally, the battery was designed to include independent measures of working memory, so that residual effects upon auditory test performance could be explicitly modeled.

3.2.2 To assess a wide range of perceptual property processes

Whilst the present battery was designed to include tests at each of the three cognitive levels previously assessed (perceptual property, apperceptive, semantic), it aimed to assess a wider range of perceptual property processes. This focus was motivated by the results of the previous chapter, in which prominent perceptual deficits were relatively auditory-specific (in progressive non-fluent aphasia; PNFA), whilst prominent semantic deficits were modality-general (in semantic dementia; SD). At the perceptual property level, the previous battery included only a single assessment of timbre processing, which furthermore was sensitive to deficits of spectral but not temporal or spectrotemporal processing. Notably, spectrotemporal deficits may account for a significant proportion of auditory impairment in dementia since relevant processes are likely to rely upon regions of non-primary auditory cortices (Altmann et al., 2010; see section 1.5.2.2.2) that are typically atrophied in syndromes such as PNFA, LPA and AD (Gorno-Tempini et al., 2004; Rohrer et al., 2009; Seeley et al., 2009; Rohrer et al., 2010b;). Thus, the present study aimed to include an assessment of timbre perception based upon spectrotemporal processing. Further tests were also designed to probe the

perceptual properties of pitch (see section 1.5.2) and auditory size (see section 1.5.2.3), which are likely to depend upon cortical areas that are relatively spared in PNFA, LPA, AD, and SD (see section 1.6). Additionally, novel auditory object apperception and semantic tests were also developed to facilitate the corroboration of previous results using alternative stimulus sets. Furthermore, the use of a new semantic test alongside more comprehensive perceptual tests was intended to facilitate further examination of associations between perceptual and semantic processing stages. Finally, whilst the previous battery had sought to reveal modality-specific effects via the inclusion of broadly comparable auditory and visual tests, the validity of this approach is reduced when assessing relatively fine-grained aspects of perceptual processing; thus, no attempt within the second battery was made to develop analogous tests in a non-auditory modality.

3.2.3 To assess a broader range of dementia syndromes

The current study aimed to assess a broader range of patient groups in order to facilitate the differentiation of disease-specific auditory deficits from more generic effects of degeneration. Thus, the syndromes of PNFA, LPA, and typical Alzheimer's disease (AD) were included, alongside healthy controls. Additionally, one patient with progranulin associated aphasia (GAA) was also examined. As previously discussed, each of these dementia syndromes involves selective damage to distinct functional networks, which may lead to specific profiles of auditory deficits; therefore, a comparison of behavioural performances between syndromes may illuminate the organisation of networks for non-verbal auditory cognition. The inclusion of AD patients was additionally motivated by the desire to include a disease control group against which to compare the PPA syndromes. AD fulfils this role because it is likely to be both behaviourally and anatomically distinct: patients may exhibit relatively greater apperceptive and semantic non-verbal auditory processing deficits (Rapcsak et al., 1989, Eustache et al., 1995; Baird and Samson, 2009; Jeon and Lee, 2009; Vanstone and Cuddy, 2010) in association with damage throughout the 'default' network (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010). Finally, given the current focus upon auditory-specific perceptual deficits, semantic dementia (SD) patients, who typically exhibit pan-modal

object recognition difficulties without any auditory perceptual impairment (see Chapter 2), were not included in the present study.

3.3 Hypotheses

Hypotheses for the current study, based on the previous literature review (Chapter 1) and the findings of Chapter 2, were as follows: (i) each of the three dementia groups included (PNFA, LPA, AD) involve distinct profiles of non-verbal auditory processing deficits; (ii) PNFA leads to predominant deficits of perceptual (property and/or apperceptive) processing; (iii) LPA leads to impairments that are similar to those found in PNFA, but with predominant deficits of apperceptive processing; (iv) AD leads to predominant deficits of apperceptive and semantic processing; (v) given that PNFA, LPA and AD involve damage to functionally coherent and distributed cortical regions that are likely to overlap with non-verbal auditory processing networks, each syndrome may also lead to subtle deficits at additional stages of cognition; (vi) impairments of working memory are likely to partially account for deficits of non-verbal auditory processing in all patient groups; (vii) LPA patients may show particularly strong effects of working memory upon non-verbal auditory processing, given evidence for prominent working memory deficits in this syndrome. In contrast, no specific hypotheses were made about the non-verbal auditory deficit profile of the single GAA patient given a current lack of evidence.

3.4 Methods

3.4.1 Subjects

Thirty-four consecutive patients fulfilling clinical diagnostic criteria for AD or PPA (excluding patients with semantic dementia) were recruited via a tertiary cognitive disorders clinic. Twenty healthy control subjects with no history of neurological or psychiatric illness also participated (data summarised in Table 3.1). The patient cohort comprised 21 patients with AD, 5 with PNFA, 7 with LPA, and one with PPA in association with a known progranulin gene mutation (here designated progranulin-associated aphasia, ‘GAA’). Patient diagnoses were based upon a structured clinical history and neurological examination by an experienced cognitive neurologist, and a general neuropsychological assessment (which also provided background data to assist interpretation of the

experimental auditory battery). A diagnosis of AD was based on revised NINCDS-ADRDA criteria for probable AD (McKhann et al.,1984; Dubois et al., 2007) with a corroborating history of episodic or topographical memory impairment as the leading symptom. All patients with PPA presented with language impairment as the leading clinical symptom. A diagnosis of PNFA was based on evidence of speech apraxia and/or agrammatism, impaired single word repetition but preserved single word comprehension and a corroborating history of progressive speech production impairment as the leading symptom (Neary et al., 1998; Gorno-Tempini et al., 2004). A diagnosis of LPA was based on a history of language-led cognitive decline with evidence of word-finding pauses in spontaneous speech (without speech apraxia), impaired repetition and comprehension of sentences (with relatively preserved repetition of single words) and impaired verbal working memory (Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2008; Rohrer et al., 2010c). Neurolinguistic findings in the patient with GAA have been previously described (Rohrer et al., 2010a): in essence, this 64 year old right-handed male shopkeeper had a four year history of gravely impoverished propositional speech with anomia, prolonged word-finding pauses, impaired speech repetition (most marked for sentences), severely impaired verbal (with preserved visuo-spatial) working memory and relatively selective impairments of verb processing and associative verbal (but preserved visual) semantic processing. Most (20/21) patients with AD were taking either an acetylcholinesterase inhibitor (donepezil or rivastigmine) or memantine at the time of testing; 3/7patients with LPA were taking donepezil while no patients with PNFA were receiving psychotropic medication. A subset of the neuropsychological assessments completed by patients, measuring general (non-auditory) cognitive abilities that might influence performance on the experimental tests, was also completed by controls. Subjects with clinically significant bilateral hearing loss were excluded from this study, and all members of the present cohort reported either no clinically significant hearing loss (N=52), or clinically significant hearing loss in one ear only (one subject from each of the AD and control groups). However, given the prevalence of age-related hearing problems in older adult populations, the effects of sub-clinical hearing loss upon assessments of auditory cognition were measured (see below). Demographic and general neuropsychological data for all subjects are summarised in Table 3.1.

All patients underwent volumetric brain MR imaging on a Siemens Trio TIM 3-Tesla scanner at the time of their participation in the study. On visual inspection, the MRI findings were in keeping with the clinical diagnosis for all patients (further details in Chapter appendix, section 3.8, Table 3.5). In the AD group, 19/21 patients had symmetric, predominantly hippocampal and mesial temporal lobe atrophy; in the PNFA group, 3/5 patients had predominantly left-sided peri-Sylvian atrophy; and in the LPA group, 6/7 patients had predominantly left-sided parieto-temporal atrophy. The patient with GAA had predominantly left-sided fronto-parieto-temporal atrophy.

Table 3.1 Demographic and neuropsychology data: summary statistics by group, and group differences

Measure	Units	Control	AD	PNFA	LPA	GAA	Group differences		
		Mean (std. dev); unless otherwise indicated				Score	AD vs. PNFA	AD vs. LPA	PNFA vs. LPA
Gender	m:f	6:14	9:12	0:5*	5:2	1 male	√		√
Age	years	65.1 (7.7)	65.0 (7.9)	68 (6.6)	64.3 (4.8)	64			
Education		13.6 (3.6)	13.5 (3.0)	12.6 (3.6)	11.3 (1.6)*	12		√	
Disease duration	months	-	71.2 (30)	51.4 (13.6)	49.3 (11.0)	774	√	√	
Medication	AChEI	-	18	0	3	None	-	-	-
	Memantine	-	2	0	0		-	-	-
MMSE	raw score / 30	-	22.1 (4.2)	19.2 (5.0)	9.4 (3.9)	0		√	√
WASI VIQ	IQ	-	101.1 (16.9)	**65.0 (15.4)**	**59.4 (7.6)**	**55**	√	√	
WASI PIQ		-	87.3 (19.4)	81.2 (12.4)	**68.9 (4.9)**	95		√	
BPVS[3]		-	109.5 (17.4)	81.4 (31.7)	**53.7 (21.9)**	112	√	√	
RMT (Words)	Z	-	-1.4 (0.6)	-0.7 (1.0)	**-1.7 (0.0)**	**-1.7**	√	√	√
RMT (Faces)		-	-1.3 (0.7)	-1.1 (0.7)	**-1.7 (0.0)**	-1.3		√	√
Graded Naming Test		-	-0.8 (1.5)	**-1.8 (1.4)**	**-2.7 (0.0)**	**-2.3**		√	√
Arithmetic		-	-1.1 (1.0)	**-1.8 (0.7)**	**-2.3 (0.1)**	**-2.3**		√	
Object Decision		-	-0.4 (1.2)	-0.8 (1.3)	-0.6 (1.2)	3.0			
Stroop (Colour naming)[1]		-	-1.5 (1.4)	**-2.5 (1.2)**	**-3.0 (0.0)**	Unable		√	
Stroop (Word reading)[1]		-	-1.2 (1.6)	**-2.5 (1.2)**	**-3.0 (0.0)**	Unable		√	
Stroop (Interference)[1, 2]		-	-1.5 (1.2)	**-2.8 (0.2)**	**-3.0 (0.0)**	Unable	√	√	
Digit span (forwards)	raw score / 12	9.8 (1.5)	7.5 (2.2)*	4.6 (3.5)*	3.3 (3.1)*	0	√	√	
Digit span (backwards)		8.2 (3)	5.2 (2.8)*	2.0 (1.9)*	1.7 (1.5)*	0	√	√	
Visuo-spatial span (forwards)		7.7 (2.2)	5.2 (2.5)*	5.0(1.0)*	2.7 (1.5)*	6		√	√
Visuo-spatial span (backwards)		7.3 (1.0)	3.9 (2.1)*	3.8 (2.2)*	1.0 (0.8)*	5		√	√
Single word repetition	raw score / 20	-	-	7.5 (9.3)[4]	18.4 (2.1)[5]	17	-	-	

Statistical inferences are based on bootstrap confidence intervals (95%, bias-corrected, accelerated with 2000 replications), and are adjusted for age and gender (except where test score standardisation had already accounted for these factors). **KEY:** Bold numbers indicate mean patient score < 5th percentile of published normative data; *, patient group significantly different to control group ($p<0.05$); √, significant difference between patient groups ($p<0.05$); -, not tested; [1], 5 LPA patients did not attempt the Stroop test; [2], 3 AD and 3 PNFA subjects did not attempt the Stroop interference condition; [3], normative data for 18 year-old subjects; [4], 1 PNFA patient did not complete the single word repetition test; [5], 2 LPA patients did not complete the single word repetition test. AChEI, acetylcholinesterase inhibitor; AD, clinically typical Alzheimer's disease; Arithmetic, Graded Difficulty Arithmetic test (Jackson and Warrington, 1986); BPVS, British Picture Vocabulary Scale (Dunn et al., 1982); Digit span, WMS-R Digit Span (Wechsler, 1987); GAA, single case with progranulin-associated aphasia (see text); Graded Naming Test, (McKenna and Warrington, 1983); LPA, logopenic aphasia; MMSE, Mini-mental state examination (Folstein et al., 1975); Object Decision test of visual object perception from the Visual Object and Space Perception Battery (Warrington and James, 1991); PNFA, progressive non-fluent aphasia; RMT, Recognition Memory Test (Warrington, 1984); Single word repetition test composed from 20 low frequency words with 1, 2 or 3 syllables selected from the word repetition test of McCarthy and Warrington, 1984 (this test was used to help define the PNFA and LPA syndromes); Stroop, D-KEFS Stroop test (Delis et al., 2001); Visuo-spatial span, WMS-III Spatial Span (Wechsler, 1997); WASI VIQ and PIQ, Wechsler Abbreviated Scale of Intelligence measures of verbal and performance IQ (Wechsler, 1999).

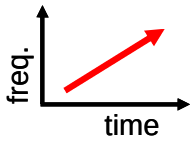
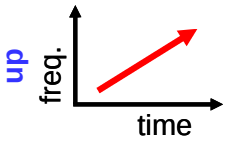
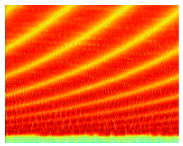
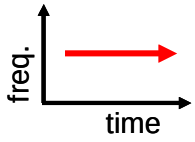
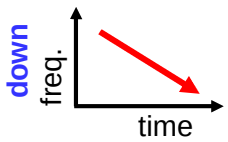
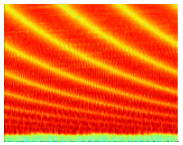
3.4.2 Peripheral hearing assessment

To assess any effects of hearing loss on performance in the experimental tasks, all subjects underwent pure tone audiometry, administered via headphones from a notebook computer in a quiet room. Five frequency levels (0.5, 1, 2, 3, 4 KHz) were assessed: at each frequency, subjects were presented with a continuous tone that slowly and linearly increased in intensity. Subjects were instructed to tap as soon as they could detect the tone; this response time was measured and stored for offline analysis. The mean value for three presentations of the same tone in the right ear (or the left ear in the case of one AD patient and one control subject who reported unilateral right-sided hearing loss) was taken as the detection threshold for that frequency.

3.4.3 Structure of the experimental battery

In designing the experimental battery, three general principles were followed: all tests used forced-choice responses, to standardise the response procedure across different levels of processing; cross-modal responses were avoided, to allow conclusions about within-modality auditory cognitive processes; and all trials presented a single auditory object, to reduce working memory demands associated with comparisons between sequentially presented sounds. The tests in the experimental battery are shown schematically in Figure 3.1 and sound examples are provided (sounds 16-29).

Figure 3.1 Schematic of experimental test battery

Test	Sub-object property					Apperceptive	Semantic
	Pitch change detection	Pitch change direction	Spectrotemporal (timbre) discrimination	Auditory size discrimination – familiar	Auditory size discrimination – unfamiliar	Degraded sound categorisation	Semantic sound categorisation
Binary response options	up 	up 	up 	big 	big unfamiliar large animal	tool degraded tool sound	inside 
	same 	down 	down 	small 	small unfamiliar small animal	animal degraded animal sound	outside 

All tests involved a binary forced choice decision procedure; the alternatives for each test are here represented diagrammatically. The pictures in the schematic are intended only to illustrate the types of sound stimuli used, and were not shown to subjects. During testing, response cards were used so that subjects could answer by pointing or speaking. For each test, response cards presented the two appropriate verbal options. In addition, in order to familiarise subjects with each test, visual diagrams were used as follows: for the pitch and timbre tests, directional arrows; for the auditory size tests, the words “big” and “small” printed in large and small font respectively; for the apperceptive test, two arrays of photos containing canonical examples of tools and animals respectively; for the semantic test, photographs of an interior and an outside scene to indicate inside and outside respectively. Sound examples for each test are also provided (numbers 19-29).

3.4.3.1 Perceptual property processing

3.4.3.1.1 Pitch change perception

Pure tones were synthesised digitally in MATLAB (MathWorks^{TM}). All tones either had constant, descending, or ascending frequency (pitch). Ascending and descending tones had a pitch excursion between 0.6-0.8 octaves, and a rate of pitch change between 0.3-0.4 octaves per second. Values of centre pitch (range: 230-270 Hz) and absolute intensity were varied between stimuli; all tones were of fixed duration (2 seconds). Two tests were based on these stimuli. In the first test (pitch change detection), constant tones and ascending tones were presented and the task on each trial was to decide if the tone changed or remained the same. In the second test (pitch change direction perception), ascending tones or descending tones were presented and the task on each trial was to decide if the tone went 'up' or 'down'. Sound examples for each test are provided (examples 16-19). Each test comprised 20 trials (10 constant, 10 changing pitch). The two pitch tests were administered consecutively.

3.4.3.1.2 Spectrotemporal modulation (timbre) perception

A test requiring perception of complex spectrotemporal structure was created in order to probe a cognitive mechanism relevant to the encoding of timbre, which is likely to be a key component of auditory object identity. Here, the perception of spectrotemporal 'ripple' sounds was examined, requiring the conjoint processing of simultaneous amplitude and frequency modulations (Chi et al., 1999). Spectrotemporal stimuli associated with a percept of continuous upward or downward sound motion were synthesised using a previously described algorithm (Chi et al., 1999) under MATLAB. Two combinations of frequency modulation (units: cycles/octave, cyc/oct) and amplitude modulation (units: Hertz, Hz) were chosen because they produce a clear percept of an upward or downward sweep: (i) 2 cyc/oct, 5 Hz; (ii) 2.5 cyc/oct, 6 Hz. Values of centre pitch (range: 230-270 Hz) and absolute intensity were varied between stimuli; all stimuli were of fixed duration (6 seconds). The task on each trial was to determine if the sound went 'up' or 'down'; sound examples are provided (examples 20-21). The timbre test comprised

20 trials (5 ‘up’ and 5 ‘down’ stimuli for each of the two modulation parameter combinations).

3.4.3.1.3 Auditory size perception

Perceived acoustic size is largely dependent upon the length of the resonant tract through which a sound is emitted (the vocal tract in the case of humans and animals: Smith et al., 2005). Specifically, vocalisations are filtered in a manner that reflects the length of the emitting vocal tract (i.e., the size of the sound source); this process occurs independently of the sound’s pitch. In order to create a test based on the perception of acoustic size, two prototype sounds corresponding to a familiar animal (barking dog) and a less familiar animal (barking sea-lion) were obtained from online databases (e.g. iStockphoto.com) and re-synthesised to create exemplars with different perceived acoustic sizes. Perceived vocal tract length (VTL) was manipulated using a previously described algorithm (Kawahara et al., 1999; Kawahara and Irino, 2005; Smith et al., 2005; von Kriegstein et al., 2006; von Kriegstein et al., 2007). During re-synthesis of stimuli, perceived VTL was scaled, whilst glottal pulse rate (pitch) was held constant. A range of VTL scaling factors was applied to each prototype sound to create 10 “large” (145-165% of original VTL) and 10 “small” (50-65% of original VTL) exemplars, corresponding to two sets of 20 stimuli. These stimulus sets were used to create two tests of auditory size perception based on the dog and the sea-lion vocalisations respectively, in order to analyse familiar and unfamiliar sounds separately. Pitch and intensity were varied and balanced across conditions: all stimuli were re-synthesized at 1 of 4 pitch values (166, 185, 203, and 222 Hz), with varying absolute root mean square intensity. Stimulus duration was fixed at 7 seconds. The task on each trial was to decide if the sound was made by a large or a small animal; sound examples are provided (examples 22-25). The two size tests were administered consecutively.

3.4.3.1.4 Apperceptive processing: perceptual categorisation of degraded natural sounds

In order to assess an apperceptive level of sound object processing, a test that required the categorisation of degraded sounds based upon perceptual rather than semantic information was designed. 40 natural sounds from two different sound

categories (20 animal calls, 20 tool noises) were selected from online sound databases (e.g. iStockphoto.com; all stimuli are listed in the Chapter appendix, section 3.8, Table 3.6). All sounds were degraded using a low-pass modulation filtering procedure, according to a previously described algorithm (Boumans et al., 2007; Elliott and Theunissen, 2009) run under MATLAB (MathWorks^{TM}). This procedure removes particular ranges of frequency and amplitude *modulations* that are relevant to the perception of environmental sounds. Unlike the more common process of filtering particular frequency ranges, modulation filtering leaves the overall spectrotemporal structure of the sound largely intact. The objective of the perceptual manipulation here was to remove sufficient auditory detail to render the identification of individual items difficult, whilst leaving enough cues to facilitate item categorisation (i.e., animal or tool). To ensure that the sound degrading procedure preserved enough information to facilitate categorisation, tool and animal sounds were modulation filtered in the acoustic domain less relevant to their perception: animal calls (for which spectral cues are generally important) were temporally filtered (i.e., amplitude modulations were removed), while tool sounds (for which temporal cues are generally important) were spectrally filtered (i.e., frequency modulations were removed). Absolute filter values were varied to achieve approximately equivalent levels of perceptual degradation across the stimulus set (filter ranges: animal sounds, 1-6 Hz; tool sounds, 0.1-1.5 cyc/Hz); subsequent analysis of control performance suggested that the overall perceptual cost of the degradation procedure was similar between animal and tool conditions (see Chapter appendix, section 3.8, Table 3.6). Sound duration ranged between 1.6 and 10.5s. Root mean square intensity was fixed for all stimuli. The task on each trial was to decide whether the sound was more like an animal calling or a tool being used; sound examples are provided (examples 26-27)

3.4.3.1.5 Semantic processing: semantic categorisation of environmental sounds

The clinical population here presented a particular challenge for the assessment of sound recognition: conventionally, recognition would be probed using a sound naming paradigm, but the interpretation of naming performance is complicated in patients with impaired word retrieval. Thus, a test that depended on specific

identification of environmental sounds but with no requirement for naming was designed. 40 recorded environmental sounds (including tool, mechanical, vehicle, and household noises) that are typically made either indoors (n=20) or outdoors (n=20) were chosen from online stimulus databases (e.g. iStockphoto.com; stimuli are listed in the chapter appendix, section 3.8, Table 3.7). All stimuli were selected to be highly familiar, clearly representative of the associated object and of high acoustic quality; subsequent analysis of control performance suggested that overall recognition levels were similar between 'inside' and 'outside' conditions (see Table 3.7). Animal calls were avoided for this test since these typically outdoor sounds contain a high level of spectral detail; this association between sound composition and semantic category might introduce a significant perceptual confound. Sound duration ranged between 2.4 and 21.8s. Root mean square intensity was fixed for all stimuli. The task on all trials was to decide whether the sound would normally be made indoors or outdoors; sound examples are provided (examples 28-29).

3.4.3.1.6 Test procedure

For each test trials were administered in a fixed randomised order. Sounds were presented as digital wavefiles from a notebook computer dichotically via Sennheiser HD 280-Pro headphones (Sennheiser, Wedeburg, Germany) at a sound pressure level of at least 70 dB. For each trial, response options were displayed in both verbal and diagrammatic form; responses could be made either by speaking or by pointing to the appropriate word/diagram (see Figure 3.1 and legend). Responses were recorded for off-line analysis. Subjects were familiarised with each task at the outset using example stimuli not used in the subsequent test; no feedback about performance was given during the test and no time limit was imposed on subject responses.

3.5 Analysis

For all tests, statistical comparisons were made between the main syndromic groups (AD, PNFA, LPA), and where appropriate, the control group using the test score as the outcome. This assumes that differences in score are treated as

equivalent regardless of the absolute performance levels at which they occur; however, this seems reasonable for these data where most controls perform at the test maxima. Bootstrap confidence intervals (95% CIs, bias-corrected, accelerated with 2000 replications) were calculated for all regression analyses in order to account for the large number of results at the text maxima, differences in between-group variance and subject effects. Bootstrapped results were additionally clustered by subject for analyses involving group by test interaction terms. The performance of the single patient with GAA was not included in any statistical analyses, and is presented for qualitative comparison purposes only.

3.5.1 General neuropsychological analysis

For the majority of tests in the general neuropsychological assessment (Table 3.1), raw results were transformed into standardised (IQ or Z) scores based on published norms for subsequent analysis. For the Mini-Mental State Examination and the single word repetition test, and for tests also completed by the experimental control group, scores were analysed in raw format. For each test, linear regression was used to assess any association of group with performance (with covariates of age and gender where score standardization had not already adequately accounted for these factors).

3.5.2 Peripheral hearing analysis

To examine the association of group with hearing, separate linear regression analyses were conducted for each of the frequency levels tested. Each model contained detection threshold as the dependent variable, and group (control, AD, PNFA, LPA) as the independent variable. Linear regression was also used to assess the relationship between scores on each auditory experimental test and peripheral hearing, with separate models for each of the frequency levels tested within each group.

3.5.3 Experimental auditory analysis

Linear regression was used to assess the main effect of group membership upon performance within each experimental auditory test, covarying for age and gender. For each of the auditory tests, two separate regression models were evaluated, with and without adjustment for reverse visuo-spatial span. Reverse visuo-spatial

span is a measure of general executive capacity and more specifically, non-verbal working memory. While the experimental auditory tests were designed to reduce working memory load, some working memory capacity is likely required for the evaluation of any sound over the interval of its duration. In an additional analysis, linear regression was used to evaluate group-by-test interactions across the whole experimental battery; in particular, this analysis sought to compare 'profiles' of test performance across the whole experimental auditory battery between groups, and in particular, to determine whether any between-group difference was disproportionately large on any individual auditory test compared to all other auditory tests combined. To facilitate the profile analysis, all raw test scores were converted, using a linear transform, to a 'scaled score' (/ 20). This additional linear regression model included the dependent measure of scaled score, fixed factors of test and group, and covariates of age, gender and reverse visuo-spatial span; bootstrap confidence intervals were clustered by subject. Finally, correlation analyses (Pearson's rho) were conducted in order to investigate associations between experimental auditory tests; specifically, all correlations between early perceptual and apperceptive tests, and between apperceptive and semantic tests were assessed. To enable the detection of distinct patterns of association in different dementia syndromes, and owing to the small sample sizes involved, these analyses were conducted within each patient group separately.

3.6 Results

3.6.1 General neuropsychological findings

Results of the general neuropsychological assessment are summarised in Table 3.1. Relative to healthy controls (represented by the current control group or expected population norms), all patient groups showed widespread deficits, but relatively intact visual object apperceptive processing (object decision). In syndromic group comparisons, the AD group showed a more severe deficit of verbal recognition memory (RMT) than the PNFA group and both aphasic groups showed more severe deficits of verbal semantic processing (BPVS) and verbal working memory (digit span) than the AD group. The LPA group showed additional

impairments of naming, recognition memory (RMT) and visuo-spatial working memory (visuo-spatial span) relative to both the AD and PNFA groups. The PNFA group showed a more severe deficit of single word repetition than the LPA group. The patient with GAA showed the previously described profile of impaired verbal processing, verbal working memory, and calculation, in the context of preserved performance IQ, visuo-spatial working memory, and visual object apperceptive processing.

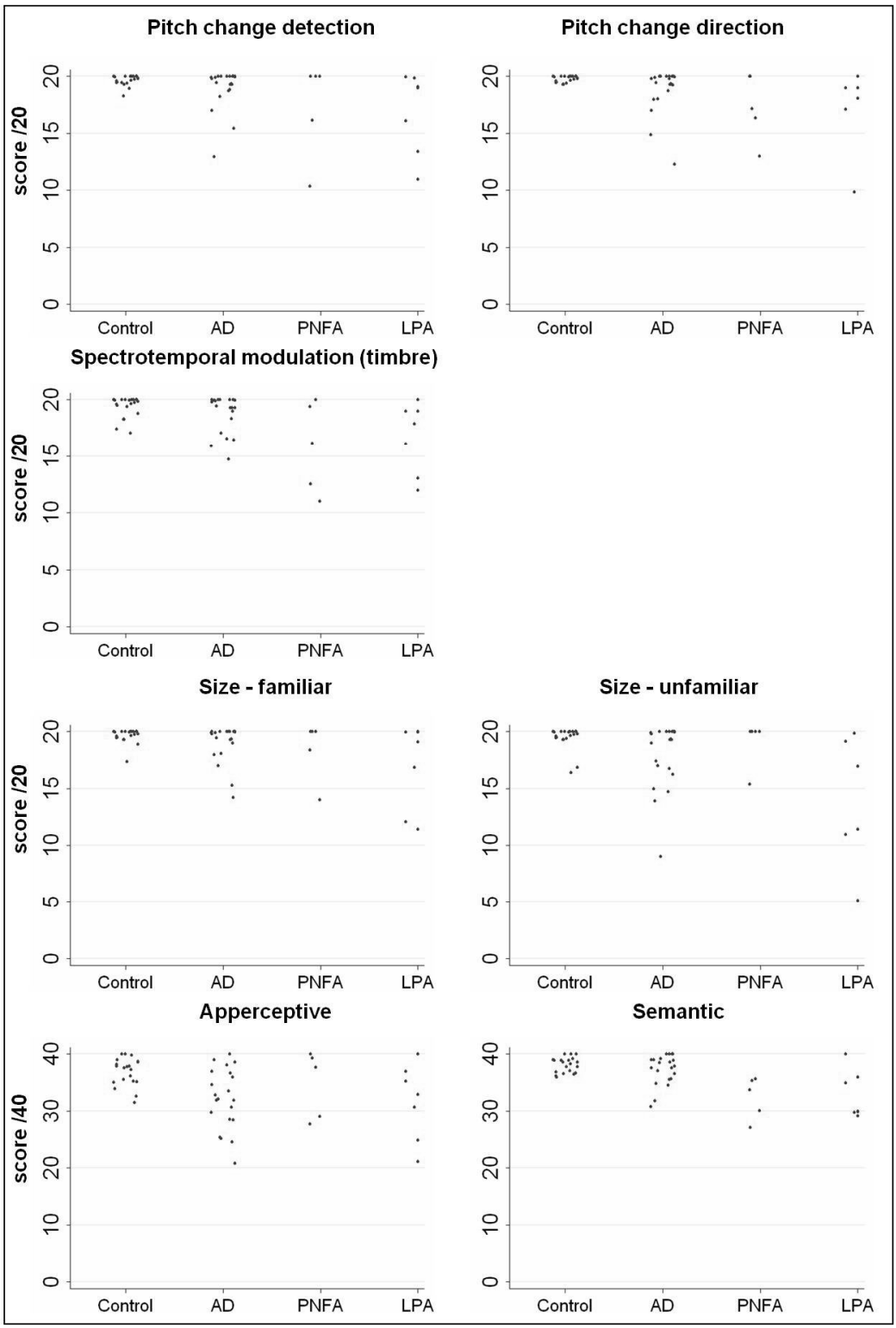
3.6.2 Peripheral hearing results

Sound detection thresholds for two of the five frequencies examined (3000 Hz, 4000Hz) did not differ for any patient group with respect to the control group (see Chapter appendix, section 3.8, Table 3.8). Detection thresholds with respect to controls were significantly increased for each patient group at 1000Hz, and also for the LPA group at 500Hz and 2000Hz. However, these differences were relatively small: intensity thresholds in patients were raised by an average value in the range of 4 - 14 dB relative to controls. The peripheral hearing results for the single patient with GAA fell within the control range. Overall the results suggest similar peripheral hearing performance across the patient and control groups, or that differences were relatively small and restricted to particular frequencies. Further, there was no evidence of a significant effect of peripheral hearing on any experimental auditory test, for any patient group or frequency level.

3.6.3 Experimental auditory findings

Auditory performance is summarised Table 3.2, and displayed in graphical form in Figure 3.2. Group differences in auditory performance are presented in Table 3.3, and group-by-test interactions are presented in Table 3.4.

Figure 3.2 Raw data for experimental auditory tests



KEY: AD, clinically typical Alzheimer's disease; LPA, logopenic aphasia; PNFA, progressive non-fluent aphasia

Table 3.2 Experimental auditory data: summary statistics by group

Test	Max. score	Control (N=20)	AD (N=21)	PNFA (N=5)	LPA (N=7)	GAA (N=1)
		Mean (std. dev.); Minimum				raw score
Pitch - detect.	20	19.9 (0.4); 19	19.0 (1.9)	17.2 (4.4)	16.7 (3.5)	20
Pitch - discrim.	20	20.0 (0.0); 20	18.9 (2.1)	17.2 (2.9)	17.6 (3.5)	18
Timbre	20	19.6 (0.8); 17	18.8 (1.9)	15.6 (4.0)	16.6 (3.4)	18
Size - fam.	20	19.9 (0.5); 18	19.1 (1.7)	18.4 (2.6)	16.9 (3.8)	20
Size - unfam.	20	19.7 (1.1); 16	18.0 (3.2)	19.0 (2.2)	13.8 (5.8)	20
Apperceptive	40	37.2 (2.6); 32	32.0 (5.5)	34.2 (5.8)	31.3 (6.3)	31
Semantic	40	38.4 (1.1); 36	37.1 (2.6)	31.8 (3.8)	32.4 (4.6)	40

NOTE: One patient with LPA did not complete the size perception test (for unfamiliar sounds); all other subjects completed all components of the experimental auditory battery. KEY: AD, clinically typical Alzheimer's disease; detect, change detection; dir, change direction perception; fam, familiar; GAA, single case with progranulin-associated aphasia (see text); LPA, logopenic aphasia; max, maximum; min, minimum; PNFA, progressive non-fluent aphasia; unfam, unfamiliar.

Table 3.3 Mean differences in test scores between groups (95% confidence intervals)

Test	Pitch – detect	Pitch - dir	Timbre	Size - fam	Size - unfam	Apperceptive	Semantic
without adjustment for reverse spatial span							
AD - control	**-0.9** (-2.1, -0.2)	**-1.2** (-2.5, -0.5)	-0.8 (-1.9, 0)	**-0.7** (-1.7, -0.1)	**-1.7** (-3.6, -0.4)	**-5.1** (-7.7, -2.4)	**-1.2** (-2.4, -0.1)
PNFA - control	-2.5 (-7.6, 0.3)	**-2.7** (-5.3, -0.7)	**-4.2** (-7.5, -1.2)	-1.5 (-4.6, 0.1)	-0.7 (-3.6, 0.9)	-3.5 (-8.8, 0.5)	**-6.5** (-10.5, -3.8)
LPA - control	**-3.4** (-6.5, -1.2)	**-2.7** (-6.3, -1.1)	**-2.9** (-5.5, -0.9)	**-2.9** (-6.2, -0.7)	**-5.8** (-11.0, -1.9)	**-5.7** (-10.7, -1.7)	**-5.9** (-8.7, -2.4)
PNFA - AD	-1.5 (-6.6, 1.4)	-1.5 (-4.2, 0.7)	**-3.4** (-6.6, -0.2)	-0.8 (-3.7, 1.1)	1.0 (-1.7, 3.8)	1.6 (-4.2, 6.2)	**-5.3** (-9.3, -2.2)
LPA - AD	**-2.5** (-5.3, -0.2)	-1.4 (-5.4, 0.2)	-2.1 (-5.0, 0.0)	-2.2 (-5.3, 0.2)	-4.1 (-9.2, 0.0)	-0.6 (-5.8, 3.8)	**-4.7** (-7.7, -0.9)
PNFA - LPA	0.9 (-4.0, 4.9)	0.0 (-2.9, 3.3)	-1.3 (-5.1, 2.4)	1.4 (-2.0, 4.7)	**5.1** (0.8, 11.1)	2.2 (-4.2, 8.3)	-0.6 (-5.3, 3.6)
with adjustment for reverse spatial span							
AD - control	-0.3 (-1.6, 1.1)	-0.8 (-4.3, 0.8)	-1.0 (-3.2, 0.7)	-0.1 (-1.4, 0.9)	-0.7 (-2.9, 1.1)	**-5.0** (-8.8, -1.3)	-0.1 (-2.1, 1.4)
PNFA - control	-1.8 (-6.0, 0.8)	**-2.3** (-5.5, -0.1)	**-4.4** (-8.1, -0.7)	-0.9 (-3.7, 0.8)	0.3 (-3.0, 2.4)	-3.4 (-9.8, 1.3)	**-5.4** (-10.6, -2.1)
LPA - control	-2.2 (-5.6, 0.9)	-2.0 (-6.7, 0.8)	**-3.3** (-7.1, -0.3)	-1.8 (-5.5, 1.0)	-4.0 (-10.2, 1.0)	-5.5 (-12.1, 2.2)	-3.9 (-8.7, 0.6)
PNFA - AD	-1.5 (-6.0, 1.5)	-1.5 (-4.0, 1.2)	-3.4 (-6.6, 0.1)	-0.8 (-3.5, 1.2)	1.1 (-1.7, 3.7)	1.6 (-3.9, 6.1)	**-5.2** (-9.5, -2.2)
LPA - AD	-1.9 (-5.1, 0.6)	-1.1 (-4.4, 0.7)	**-2.3** (-5.1, -0.2)	-1.7 (-5.0, 0.8)	-3.3 (-8.9, 1.3)	-0.5 (-6.0, 5.1)	-3.8 (-7.5, 0.1)
PNFA - LPA	0.4 (-4.8, 4.8)	-0.3 (-3.4, 3.6)	-1.1 (-4.7, 3.1)	0.9 (-2.7, 4.5)	4.4 (-0.1, 10.6)	2.1 (-4.6, 8.7)	-1.5 (-6.5, 2.9)

Statistical inferences are based on bootstrap confidence intervals (95%, bias-corrected, accelerated with 2000 replications). All analyses are adjusted for age and gender. **KEY:** Bold numbers indicate significant differences ($p<0.05$) between groups; AD, clinically typical Alzheimer's disease; detect, change detection; dir, direction perception; fam, familiar; CI, confidence interval; LPA, logopenic aphasia; PNFA, progressive non-fluent aphasia; unfam, unfamiliar.

Table 3.4 Auditory performance profiles of patient groups: between-test comparisons

Group comparison	Experimental auditory test						
	Pitch - detect	**Pitch - dir**	**Timbre**	**Size - fam**	**Size - unfam**	**Apperceptive**	**Semantic**
AD - control	0.4	0.1	0.5	0.5	-0.6	**-1.6**	0.3
	(-0.3, 1.1)	(-0.8, 0.8)	(-0.4, 1.4)	(-0.1, 1.1)	(-1.8, 0.5)	(-2.9, -0.1)	(-0.1, 0.9)
PNFA - control	-0.4	-0.5	**-1.9**	**1.0**	**2.0**	1.0	-0.8
	(-2.5, 1.3)	(-1.1, 0.1)	(-4.4, -0.2)	(0.3, 1.8)	(0.8, 3.4)	(-1.8, 3.5)	(-2.0, 0.9)
LPA - control	0.2	1.1	0.4	0.4	-2.9	0.4	0.4
	(-2.8, 2.6)	(-1.4, 3.1)	(-1.4, 2.2)	(-2.3, 2.6)	(-7.0, 1.3)	(-1.7, 2.6)	(-1.3, 1.9)
PNFA - AD	-0.8	-0.6	**-2.4**	0.5	**2.5**	2.6	-1.2
	(-3.0, 0.9)	(-1.6, 0.4)	(-4.8, -0.5)	(-0.3, 1.5)	(1.0, 4.2)	(-0.3, 5.2)	(-2.5, 0.6)
LPA - AD	-0.2	1.0	-0.1	-0.1	-2.3	2.0	0.1
	(-3.2, 2.4)	(-1.4, 3.2)	(-2.0, 1.9)	(-3.0, 2.1)	(-6.4, 1.8)	(0.0, 4.7)	(-1.7, 1.7)
PNFA - LPA	-0.6	-1.6	-2.3	0.6	**4.9**	0.5	-1.2
	(-3.8, 2.7)	(-3.6, 0.9)	(-5.4, 0.1)	(-1.8, 3.4)	(0.5, 9.0)	(-2.8, 3.6)	(-3.2, 1.5)

Statistical inferences are based on bootstrap confidence intervals (95%, bias-corrected, accelerated with 2000 replications). Figures represent the additional difference in score between groups for a given test compared to the mean difference in score between groups for all the other tests combined (with 95% confidence intervals), after accounting for age, gender and working memory; test scores have been scaled to a maximum of 20. **Key:** Bold numbers indicate significant group differences ($p<0.05$); AD, clinically typical Alzheimer's disease; detect, change detection; dir, direction perception; fam, familiar; LPA, logopenic aphasia; PNFA, progressive non-fluent aphasia; unfam, unfamiliar.

3.6.3.1 AD versus controls

The AD group was significantly impaired relative to the healthy control group on all auditory cognitive tests except timbre perception (Table 3.3). However, only the auditory apperceptive deficit remained after adjusting for nonverbal working memory performance. Additionally, the profile analysis revealed a significant group by test interaction effect which indicated a particularly severe deficit of apperceptive processing in AD: the mean AD-control score difference was on average 1.6 points greater than the mean AD-control score differences across the other tests combined (Table 3.4). In contrast to these deficits, the AD group did not differ from controls on the test of timbre perception.

3.6.3.2 PNFA versus controls

The PNFA group was significantly impaired relative to the healthy control group on tests of pitch direction perception, timbre perception and auditory semantic processing (Table 3.3). These deficits remained after adjusting for nonverbal working memory performance. Additionally, the profile analysis revealed a significant group by test interaction effect which indicated a particularly severe deficit of timbre processing in PNFA: the mean PNFA-control score difference on the timbre test was on average 1.9 points greater than the mean PNFA-control differences across all other auditory tests combined (Table 3.4). In contrast to these deficits, the PNFA group did not differ from controls on the tests of auditory size perception and auditory apperception.

3.6.3.3 LPA versus controls

The LPA group was significantly impaired relative to the healthy control group on all auditory cognitive tests (Table 3.3). However, only the timbre perception deficit remained after adjusting for nonverbal working memory performance. Additionally, the profile analysis revealed no significant group by test interaction effects involving the LPA group, providing no evidence of disproportionate impairment on any particular auditory test (Table 3.4).

3.6.3.4 Comparisons between syndromic groups

The PNFA group was significantly impaired relative to the AD group on the timbre and semantic processing tests (Table 3.3); only the deficit on the semantic test remained after adjusting for nonverbal working memory performance. The LPA group was significantly impaired relative to the AD group

on the pitch change detection and auditory semantic processing tests and impaired relative to the PNFA group on perception of auditory size information from less familiar sounds; however, these differences were no longer significant after adjusting for nonverbal working memory performance.

The profile analysis revealed a significant group by test interaction effect indicating a particularly severe deficit of timbre processing in PNFA compared to AD (the difference in mean score between PNFA and AD is 2.4 points greater for this test compared to the difference in mean score between these groups on all other tests combined; Table 3.4). Additionally, there was also a significant group by test interaction effect indicating a particularly severe deficit in the perception of auditory size from less familiar sounds in LPA compared to PNFA (the difference in mean score between PNFA and LPA is 4.9 points greater for this test compared to the difference in mean score between these groups on all other tests combined; Table 3). However, wide confidence intervals mean that these results should be interpreted with caution.

3.6.3.5 GAA

The single patient with GAA performed within the control range on most experimental auditory tests, with the exception of pitch direction perception and apperceptive processing. Of note, his performance was flawless on tests of pitch change detection, size perception, and semantic processing.

3.6.3.6 Correlations between experimental auditory tests

In separate within-group correlation analyses, no significant correlations were identified between auditory property and apperceptive performance or between apperceptive and semantic performance in any of the groups (all $p>0.05$).

3.7 Discussion

3.7.1 Syndrome-specific profiles of non-verbal auditory processing impairment

This study demonstrates that dementia syndromes are associated with deficits of non-verbal auditory processing. Additionally, evidence suggests that particular syndromes may show distinct profiles of impairments. Thus, relative to healthy subjects, patients with AD had a deficit of apperceptive processing,

patients with PNFA had a deficits of pitch direction, timbre and semantic processing, and patients with LPA had deficits of timbre processing; furthermore, these deficits were not substantially changed by accounting for working memory performance. Auditory semantic processing in PNFA and timbre processing in LPA were also impaired relative to another neurodegenerative syndrome (AD), and again, these effects were not simply attributable to working memory. For both the PNFA and AD groups, performance profiles across the whole auditory test battery corroborated the findings for each test considered separately: on the profile analysis, patients with AD and PNFA were disproportionately impaired on measures of apperceptive and timbre processing respectively. In addition, evidence suggested that these patient groups showed distinct patterns of relative cognitive preservation: AD patients had intact timbre perception, while PNFA patients had intact auditory size perception. In addition, PNFA patients did not differ significantly from controls on the apperceptive test, indicating further cognitive preservation; however, given that the group difference here was relatively large, this finding should be interpreted with caution. Taken together, the results of this study concur with those of the previous chapter in suggesting that dementia syndromes are associated with distinctive profiles of auditory object processing.

3.7.2 Syndrome-specific profiles: implications for the organisation of non-verbal auditory cognition

Current findings indicate that AD may lead to a relatively selective deficit of apperceptive processing. Whilst little previous evidence specifically supports this claim, AD has been associated with a spectrum of non-verbal auditory deficits that could potentially reflect the effects of a primary apperceptive impairment (e.g., Rapcsak et al., 1989; Eustache et al., 1995; Testa et al., 2001; Baird and Samson, 2009; Jeon and Lee, 2009; Vanstone and Cuddy, 2010). Additionally, apperceptive environmental sound agnosia has been associated with focal damage involving the posterior temporal and parietal cortices (Fujii et al., 1990; Saygin et al., 2010) that are sites of disease involvement in AD. Thus, current evidence for a relatively selective auditory apperceptive deficit in AD may indicate the relative independence of corresponding processes in the healthy brain. This dissociation of auditory apperceptive processing is also

supported by the observation of the patient with GAA, who showed impaired apperceptive but intact semantic processing; however caution is required when interpreting the performance of this single case. Additionally, previous neuropsychological evidence also suggests the relative dissociation of apperceptive processing from further stages of auditory object cognition (Schnider et al., 1994; Vignolo, 2003). However, the selectivity of the auditory apperceptive deficit in AD remains to be defined. For example, although the current AD group showed intact visual apperceptive processing (Table 3.1: Object Decision), previous studies suggest that this syndrome may lead to visual apperceptive deficits (Mendez et al., 1990; Uhlhaas et al., 2008), raising the possibility that AD may involve a modality-general impairment of apperceptive object representation; thus, further investigations are required to determine the modality-specificity of the auditory apperceptive deficits observed here, and the extent to which apperceptive mechanisms are shared between modalities. Additionally, the current AD group exhibited less severe auditory perceptual and semantic deficits, which may have influenced apperceptive performance even though correlations between apperceptive and other auditory cognitive functions were not observed. Given that AD involves selective damage to functionally coherent cortical regions (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010), the observation of parallel deficits may indicate that non-verbal auditory cognition takes place within a distributed network involving interactions between apperceptive and related processes; notably, this conclusion is supported by previous neuropsychological and neuroimaging studies (Clarke et al., 1996; Staeren et al., 2009). Thus, further research is required to determine the extent to which auditory apperceptive processing is selectively impaired in AD, and by inference, the degree of independence that it shows in relation to other stages of auditory cognition.

As already described, the PNFA group exhibited deficits of pitch direction, timbre and semantic processing which were not substantially changed by accounting for working memory performance. However, statistical analyses suggested that the deficit of timbre processing was more severe than those observed in all other tests. Notably, this finding converges with the evidence of the previous chapter, which indicated a timbre deficit in a distinct PNFA group

using an alternative neuropsychological measure. Thus, available evidence suggests that PNFA may lead to a primary deficit of timbre perception. Since timbre is a multi-dimensional spectrotemporal sound property, such a deficit may reflect an underlying difficulty in the representation of complex spectrotemporal information (see section 1.5.2.2). Additionally, the relatively selective impairment of timbre perception in this neurological group might suggest that corresponding processes in the healthy brain show relative independence. Notably, these conclusions align with previous neuropsychological evidence for selective timbre processing deficits (Mazzucchi et al., 1982; Kohlmetz et al., 2003; Griffiths et al., 2007), and previous neuroimaging evidence describing cortical regions that are specialised for particular aspects of spectral, temporal and spectrotemporal processing (Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010).

In contrast to observed timbre deficits, parallel semantic deficits in the current PNFA group were relatively less prominent. However, they were more evidently modality- and syndrome-specific in this disease group compared to all others, in line with similar evidence from the previous chapter (using an alternative test procedure). On the basis of current data alone it is not possible to establish whether the overall performance profile of PNFA reflects independent perceptual and semantic deficits, or a primary perceptual property processing disorder that gives rise to impairments at related cognitive stages. However, a range of previous literature suggests that auditory cognition involves the serial flow of information between increasingly complex stages of processing (Rauschecker et al., 1998; Binder et al., 2000; Wessinger et al., 2001; Griffiths and Warren, 2004). Therefore, it may be suggested that semantic impairments observed in PNFA are caused by the cascading effects of a primary perceptual property processing disorder, particularly since current observations emphasise the predominance of perceptual impairments. Although no correlations between perceptual and semantic tests were observed here, this conclusion may further indicate that corresponding stages of non-verbal auditory processing are interdependent. This particular notion is strengthened by previous observations that PNFA involves damage to a functionally coherent peri-Sylvian network (Seeley et al., 2009) which overlaps with areas implicated in diverse non-verbal auditory processes (Zatorre and Belin, 2001; Lewis et al., 2006; Staeren et al.,

2009; Altmann et al., 2010; Leaver and Rauschecker, 2010). It also aligns with the neuroimaging literature which suggests that semantic processing is at least partly contingent on perceptual mechanisms (see section 1.5.5.6.2; Staeren et al., 2009; Leaver and Rauschecker, 2010), and the neuropsychological literature which suggests that disorders of sound recognition are rarely selective, and tend to occur alongside perceptual deficits (see section 1.5.5.4; Clarke et al., 1996). Thus, available data indicate that PNFA may involve a primary impairment of non-verbal auditory property processing, in particular for the representation of complex spectrotemporal information, which also leads to additional semantic impairments via bottom-up neural connections within a distributed network.

The current observation of unimpaired performance in the PNFA group on the auditory apperceptive task was both unexpected and apparently at odds with results of the Chapter 2. However, this apparent discrepancy may indicate that there is no single cognitive operation that corresponds to 'auditory apperceptive processing': rather, there may exist several intermediate processing stages that might in principle be differentially vulnerable to particular profiles of cortical atrophy or neuropsychological impairment. In particular, this suggestion aligns with the view (already advanced in section 1.5.3) that auditory apperceptive agnosia may encompass a spectrum of heterogeneous disorders.

Auditory cognitive performance was influenced by working memory capacity across a range of tasks and in each syndromic group. Additionally, this factor appeared particularly relevant to the rather general impairment of non-verbal auditory functions exhibited by patients with LPA, consistent with previous evidence for auditory verbal working memory deficits in this group (e.g. Gorno-Tempini et al., 2008). Given the general requirement for tracking auditory information as it evolves over time, working memory mechanisms are likely a priori to be relevant to non-verbal auditory processing even (as in the tests here) during the perception of single auditory stimuli; for example, when labelling the direction of a pitch glide. Additionally, findings indicate that such working memory mechanisms are shared with processing in another (visuo-spatial) modality, and this interpretation is supported by functional imaging evidence in healthy subjects (Rama and Courtney, 2005; Protzner and

McIntosh, 2007; Protzner et al., 2009). While little is known about non-verbal auditory working memory processes, the present results suggest the presence of close interdependencies between mechanisms of non-verbal auditory cognition and working memory in the healthy brain; additionally, the derivation of this conclusion from a study involving dementia patients who typically exhibit damage to functionally coherent neural networks (Seeley et al., 2009), adds further weight to this conclusion.

Finally, the performance of the single patient with GAA provided further insight into cognitive mechanisms of non-verbal auditory processing. Notwithstanding his severe verbal deficits, this patient showed remarkably preserved performance on several non-verbal auditory measures (pitch change detection, size perception, semantic processing) with a relatively mild deficit of pitch direction processing and a more severe deficit of auditory apperceptive function. This general preservation in the context of a strongly asymmetric (impaired verbal, preserved non-verbal) aphasic syndrome suggests that non-verbal auditory processing is not dependent upon linguistic processes including verbal working and long term memory; however, as already emphasised, conclusions from the examination of this single case must be extrapolated with care.

3.7.3 Syndrome-specific profiles: anatomical bases

The syndrome-specific profiles of non-verbal auditory impairment observed here are consistent with previous descriptions of syndrome-specific atrophy patterns. The most robust auditory deficits observed involved relatively complex stages of auditory object processing (apperceptive processing in AD; timbre and semantic processing in PNFA; timbre processing in LPA), whereas deficits in the processing of auditory properties such as pitch and size were less prominent or less specific. Correspondingly, in these syndromes there is relative sparing of areas (including primary auditory and adjacent cortices) previously implicated in processing auditory properties such as pitch and size in both healthy subject groups (Gutschalk et al., 2002; Patterson et al., 2002; Penagos et al., 2004; von Kriegstein et al., 2006; von Kriegstein et al. 2007;) and neuropsychological patients (Tanaka et al., 1987; Zatorre, 1988; Habib et al., 1995; Lechevalier et al., 1995; Johnsrude et al., 2000; Tramo et al., 2002; Hattiangadi et al., 2005; Terao et al., 2006). In contrast, timbre processing, a multi-dimensional

spectrotemporal sound property, depends on more complex computations within a postero-lateral temporal lobe network extending from primary auditory cortex to planum temporale and the superior temporal sulcus (Warren et al., 2005a; Griffiths et al., 2007; Kumar et al., 2007). These regions are likely to be damaged in both PNFA and LPA, providing a substrate for the relatively prominent deficits of timbre processing that we have described here. Mechanisms of apperceptive and semantic processing are likely to be mediated by distributed overlapping cerebral networks traversing postero-lateral temporal and inferior parietal cortices (Lewis et al., 2005; Engel et al., 2009; Staeren et al., 2009; Lewis et al., 2010; Leaver and Rauschecker, 2010), and AD and PNFA are likely to involve distinct patterns of damage within these areas (e.g., Seeley et al., 2009). Together this evidence therefore suggests an anatomical basis for the differing profiles of auditory cognitive performance observed in these syndromes. Furthermore, previously proposed networks of non-verbal auditory processing are supported by the current evidence for multiple parallel auditory impairments in dementia patients who typically exhibit damage to functionally coherent cortical regions (Seeley et al., 2009). However, further research involving correlative structural and functional imaging will be required to specify substrates in more detail.

3.7.4 Study limitations and suggestions for future work

This study has the limitations of small case numbers and a lack of direct anatomical correlation with behavioural deficits. Furthermore, the impairments highlighted occurred in the context of more generalised auditory dysfunction and more widespread cognitive impairment, and none were restricted to a particular dementia syndrome. Taking these caveats into account, the evidence presented here should motivate future work in larger patient cohorts and additional neurodegenerative diseases. For example, more detailed descriptions of the distinct profiles of non-verbal auditory impairment in different dementia syndromes are required to enhance the understanding and management of corresponding symptoms. Additionally, there is a need to establish the strength and direction of relations between different stages of non-verbal auditory processing, for example, between perceptual and semantic mechanisms. Finally, structural and functional neuroimaging will be required to correlate auditory deficits with patterns of network-specific atrophy in dementia,

and ultimately, such work should help to illuminate networks of non-verbal auditory processing.

3.7.5 Discussion summary

Current data, like the findings of the previous chapter, indicate that dementia syndromes are associated with distinctive profiles of auditory object processing. From a cognitive neuropsychological perspective, evidence suggests that stages of non-verbal auditory cognition show both degrees of independence, and close interdependencies with other processes (although the directions of such links remain to be established). Further, the derivation of these conclusions from a study of dementia patients who typically exhibit damage to functionally coherent neural networks (Sonty et al., 2007; Buckner et al., 2009; Meslaum, 2009; Seeley et al., 2009; Zhou et al, 2010), suggests that non-verbal auditory processing may be mediated by distributed and reciprocally connected networks, which show varying degrees of functional specialisation.

3.8 Chapter appendix

Table 3.5 Summary of MRI findings in patient groups

Group	No. of cases	MRI findings
AD	19	symmetric atrophy, more marked in hippocampi and mesial temporal lobes
	1	diffuse atrophy without hippocampal emphasis
	1	normal for age
PNFA	3	predominantly left-sided peri-Sylvian atrophy
	1	frontotemporal atrophy, no cerebral asymmetry
	1	diffuse atrophy, no cerebral asymmetry
LPA	6	predominantly left-sided parieto-temporal atrophy
	1	symmetric atrophy, more marked in hippocampi
GAA	1	predominantly left-sided fronto-parieto-temporal atrophy

KEY: AD, clinically typical Alzheimer's disease; GAA, progranulin associated aphasia; LPA, logopenic aphasia; PNFA, progressive non-fluent aphasia

Table 3.6 Stimuli used in the apperceptive sound categorisation test

Animals		Tools	
Sound	**Controls (%)**	**Sound**	**Controls (%)**
cat meowing (1)	90	axe chopping wood	95
cat meowing (2)	80	chopping with a kitchen knife	95
cat meowing (3)	100	cutting ice with a pickaxe	100
cockerel calling	100	dispensing sellotape	100
cow mooing	100	filing wood	100
crow calling	95	hammering (1)	100
dog barking (1)	100	hammering (2)	100
dog barking (2)	95	mixing with a wooden spoon in a bowl	85
dog whimpering	100	peeling a vegetable with a peeler	85
dog yelping	85	punching a hole in paper	100
duck quacking	95	sanding wood with sandpaper	100
geese calling	70	sawing wood	100
monkey calling	100	scissors cutting paper	100
pig squealing	80	scraping the ground with a shovel	100
puppies whimpering	90	spoon stirring in cup	50
sea lion barking (1)	80	stapling paper	95
sea lion barking (2)	90	sweeping with a broom	95
sea lion barking (3)	90	typing with a mechanical typewriter	100
sheep calling (1)	100	whisking liquid in a bowl	95
sheep calling (2)	100	writing with chalk on a blackboard	85

KEY: Controls (%), the percentage of healthy control subjects correctly categorising the item as either a tool or an animal (an index of difficulty of apperceptive processing). Control performance did not differ significantly for categorization of animal versus tool sounds (Mann-Whitney U test, p=0.23).

Table 3.7 Stimuli used in the semantic sound categorisation test

Inside		Outside	
Sound	**Controls (%)**	**Sound**	**Controls (%)**
brushing teeth with a toothbrush	95	boat horn sounding	100
chopping food with a knife (1)	95	car horn sounding	100
chopping food with a knife (2)	90	car starting	100
cuckoo clock sounding	100	chainsaw being used	95
electronic clock alarm sounding	100	chopping a tree down with an axe	100
footsteps on wooden floor	100	emergency vehicle siren sounding	100
gurgling from a kitchen sink	100	fireworks	100
kitchen cutlery clattering together	100	footsteps in grass	100
kitchen plates clattering together	90	footsteps on gravel	100
manual typewriter being used	100	helicopter engine running	80
scissors cutting paper	90	horse galloping	95
stapler being used	70	lawnmower engine running	100
stirring in a cup with a spoon	100	lawnmower starting	100
tap running into a sink	80	pickaxe bring used	95
tapping a cup with a spoon	100	rain on a pavement	90
telephone ringing	100	raking dirt	100
toilet flushing	100	scraping shovel on icy driveway	95
vacuum cleaner	100	shoveling gravel	100
washing machine spinning	85	train horn sounding	100
whisking in a bowl	100	waves lapping on a shore	95

KEY: Controls (%), the percentage of healthy control subjects correctly categorising the item as either ‘inside’ or ‘outside’ (an index of difficulty of stimulus identification). Control performance did not differ significantly for categorization of ‘inside’ versus ‘outside’ sounds (Mann-Whitney U test, p=0.47).

Table 3.8 Peripheral hearing: effect of syndromic group on sound detection threshold versus healthy controls

Freq. (Hz)	Group	Mean difference* (s)	95% CI (s)	
			Lower	Upper
500	**AD**	2.9	-0.6	6.2
	PNFA	6.6	-2.7	21.3
	LPA	**8.2**	1.3	14.7
1000	**AD**	**3.3**	0.7	5.1
	PNFA	**7.9**	3.5	16.4
	LPA	**11.1**	4.7	20.6
2000	**AD**	3.0	-0.6	7.6
	PNFA	1.6	-2.4	6.8
	LPA	**5.7**	0.6	12
3000	**AD**	-0.5	-5.1	4.9
	PNFA	0.0	-6.5	7.6
	LPA	0.1	-5.6	9.3
4000	**AD**	4.5	-3.5	12.5
	PNFA	0.7	-9.4	11.9
	LPA	6.2	-6.5	23.1

Statistical inferences are based on bootstrap confidence intervals (95%, bias-corrected, accelerated with 2000 replications). **KEY:** Bold numbers indicate significant group differences ($p<0.05$); *, all differences are for the syndromic group versus the healthy control group; AD, clinically typical Alzheimer's disease; CI, confidence interval; LPA, logopenic aphasia; PNFA, progressive non-fluent aphasia.

4 Distinct patterns of non-verbal auditory cognitive impairment in two cases of primary progressive aphasia

4.1 Summary

This chapter presents a symptom-led study of two patients (Cases 1 and 2) with distinct syndromes of primary progressive aphasia (PPA), who exhibited prominent non-verbal auditory impairments at initial assessment. Both patients completed a comprehensive neuropsychological battery designed to assess property, apperceptive, and semantic stages of non-verbal auditory processing; additionally, each patient was assessed using additional tests designed to probe their individual auditory impairments in detail. Whilst Case 1 exhibited relatively selective deficits for the perception of 'basic' auditory properties (pitch, loudness), Case 2 showed a relatively selective impairment of 'complex' auditory property (timbre) perception, i.e., dystimbria. Taken together, these cases provide evidence for a double dissociation between mechanisms of basic and complex auditory property processing. Further, the detailed examination of deficits shown by each patient provides insight into both auditory perceptual property processing disorders in PPA, and the organisation of corresponding cortical mechanisms in the healthy brain.

4.2 Background

This chapter presents a symptom-led study of two patients with distinct syndromes of primary progressive aphasia (PPA) and distinct profiles of non-verbal auditory impairment. In Case 1, a patient with logopenic (phonological) aphasia (LPA), the leading auditory symptom was impaired discrimination of relatively basic auditory properties such as pitch. In Case 2, a patient with progressive non-fluent aphasia (PNFA), the leading auditory symptom was impaired comprehension of auditory objects (and particularly words), despite relatively preserved object comprehension in other modalities. The present study comprised a series of non-verbal auditory experiments designed to reveal the cognitive mechanisms underlying each patient's deficits. Adopting the theoretical approach described in Chapters 2 and 3, a novel neuropsychological battery was designed to assess property, apperceptive, and semantic stages of non-verbal auditory processing in both patients in comparison to age-matched healthy controls. Additionally, each patient was assessed with further tests to probe their individual auditory impairments in more detail. It was hypothesised that Cases 1 and 2 would show distinct profiles of auditory deficits in association with different patterns of cortical damage.

4.3 Subjects

4.3.1 Case 1

Case 1 is a right handed woman who was 69 at the time of testing. She left school at age 15 with no qualifications, and worked as a dress machinist, a sales assistant, and most recently, a filing clerk for a major bank. Case 1 presented to the specialist cognitive disorders clinic at the National Hospital for Neurology and Neurosurgery (NHNN) with anomia, episodic memory impairment, and a profound deficit of auditory verbal working memory. She was diagnosed with primary progressive aphasia (PPA) of the logopenic (phonological) subtype (LPA) according to received clinical criteria (Gorni-Tempini et al., 2004; Gorni-Tempini et al., 2008; Gorni-Tempini et al., 2011). Case 1 was subsequently recruited to a group study of non-verbal auditory object processing (Chapter 2), but was unable to participate due to severe deficits in the perception of basic sound properties (e.g., pitch). Although Case

1 never received formal musical training, her family report that she could sing in tune as a child; it is therefore unlikely that she suffers from congenital amusia (Stewart et al., 2006). Formal audiometry revealed normal hearing levels (age-corrected). A volumetric structural MR brain image showed bilateral but predominantly left sided peri-Sylvian atrophy with diffuse involvement throughout frontal, temporal and parietal lobes and particular damage to regions surrounding the temporo-parietal junction including the planum temporale (Figure 4.1).

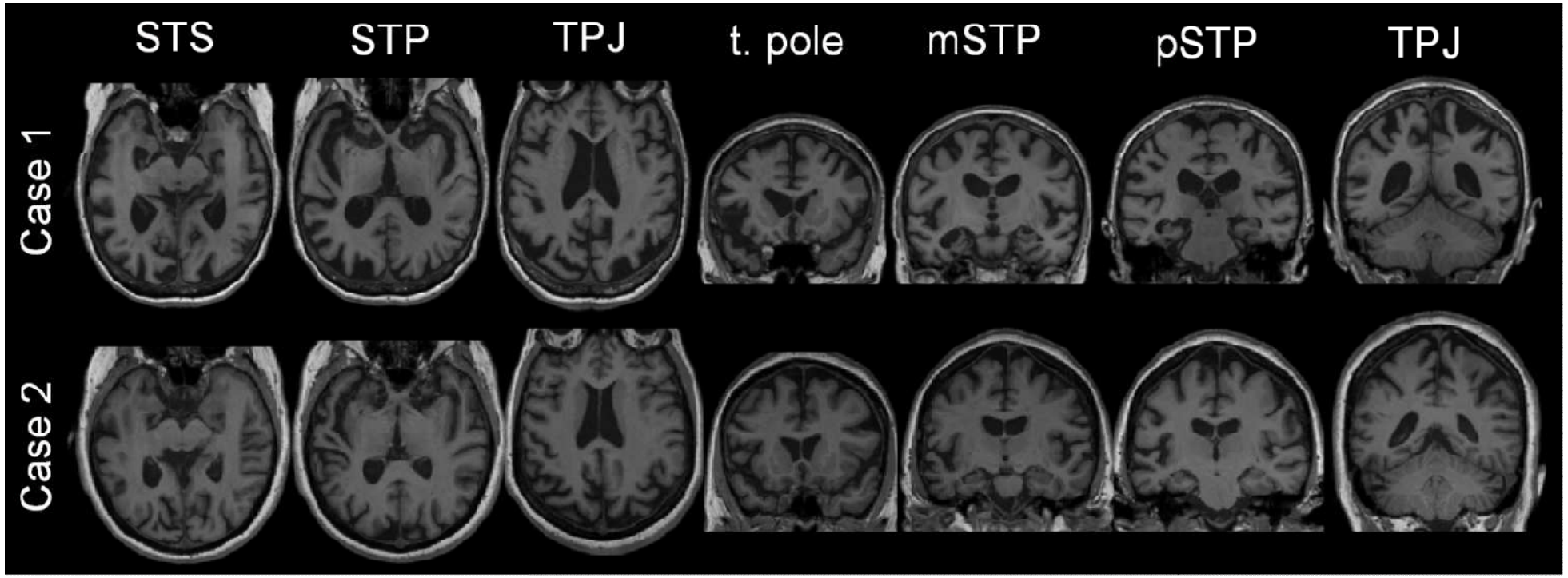
4.3.2 Case 2

Case 2 is a left handed woman who was 66 at the time of testing. She left school at age 15 with no qualifications, and worked as a comptometer operator, and more latterly, an administrator. She presented to the specialist cognitive disorders clinic at the NHNN with dysarthric, effortful speech and was diagnosed with primary progressive aphasia (PPA) of the progressive non-fluent aphasia (PNFA) subtype (Neary et al., 1998; Gorno-Tempini et al., 2011). Additionally, she exhibited profound difficulties in the comprehension of auditory objects, and particularly speech, despite preserved comprehension of written verbal material; thus Case 2 also fulfilled clinical criteria for word deafness, i.e., a relatively selective deficit for the perception of speech sounds (e.g., Auerbach et al., 1982; see section 1.5.3.3). Although Case 2 never received formal musical training, her husband reports that she enjoyed listening to music prior to the onset of her illness and was not tone deaf; it is therefore unlikely that she suffers from congenital amusia. Formal audiometry revealed normal hearing levels (age-corrected). A volumetric structural MR brain image showed bilateral but predominantly left sided peri-Sylvian atrophy, with particularly prominent involvement of the left anterior superior temporal gyrus (Figure 4.1).

4.3.3 Controls

Four groups of healthy controls, without any previous neurological or psychiatric conditions, clinically significant hearing problems, or tone-deafness, participated in different sections of this study; demographic details are presented in Table 4.7 in the chapter appendix.

Figure 4.1. Volumetric structural MR images of Cases 1 and 2 showing key cortical landmarks



Slices of volumetric structural MR images acquired using a T1-weighted 3D MDEFT sequence (Deichmann et al., 2004) with a Siemens Trio TIM 3-Tesla scanner, showing key auditory processing landmarks in Cases 1 and 2. For all slices, the left hemisphere is shown on the left, and axial slices are parallel to the superior temporal plane. KEY: m, middle; p, posterior; STS, superior temporal sulcus; STP, superior temporal plane; TPJ, temporo-parietal junction; t. pole, temporal pole.

4.4 Background neuropsychological assessments

4.4.1 Background neuropsychological assessments: Methods

Both patients completed a comprehensive neuropsychological battery (Table 4.1). Patient scores were transformed into standardised scores using normative data where available.

4.4.2 Background neuropsychological assessments: Results

In background neuropsychological assessments, Case 1 showed impairments across multiple cognitive domains (Table 4.1). Her deficits therefore accord with previous reports of LPA, which emphasise prominent verbal working memory deficits despite initially preserved single word repetition, and increasingly widespread impairment with disease progression (Henry and Gorni-Tempini, 2010; Gorni-Tempini et al., 2004; Gorni-Tempini et al., 2008; Gorni-Tempini et al., 2011; Rohrer et al., 2010b). However, Case 1 performed normally in the discrimination of speech syllable pairs (PALPA), indicating some preservation of auditory perceptual and working memory mechanisms for phonological information.

In background neuropsychological assessments, Case 2 generally showed impaired verbal and preserved non-verbal performance (Table 4.1). This pattern, and particularly the gross impairment of single word repetition, supports a diagnosis of PNFA (Neary et al., 1998; Gorno-Tempini et al., 2011). Additionally, whilst her impaired discrimination of speech syllable pairs (PALPA) may in part reflect her reduced auditory verbal working memory capacity (as measured in the digit span test), it might signal an additional auditory verbal perceptual deficit.

Table 4.1 Background neuropsychological assessments

Test (score format)	Case 1	Case 2
MMSE (raw /30)	10	15
Disease duration (years)	6.7	3.2
WASI - VIQ (IQ)	**69**	**55**
WASI - PIQ (IQ)	**69**	100
RMT - words (Z)	**-1.7**	**-1.7**
RMT - faces (Z)	**-1.7**	-0.7
Digit span - forwards (Z)	-0.7	**-2.7**
Digit span - backwards (Z)	**-1.7**	**-1.7**
Spatial span - forwards (Z)	**-1.7**	-1.0
Spatial span - backwards (Z)	**-2.7**	-0.7
Single word repetition (raw /20)	20*	0
PALPA 1 - same (Z)	0.5	**-31.6**
PALPA 1 - different (Z)	0.4	**-3.0**
PALPA 2 - same (Z)	0.6	**-22.5**
PALPA 2 - different (Z)	-0.3	**-4.2**
Schonell reading (Z)	-1.5	-1.5
Synonyms - concrete[1] (Z)	**-2.4**	**-3.1**
Synonyms - abstract[1] (Z)	**-2.4**	**-3.2**
GNT (Z)	**-2.7**	**-2.7**
BPVS (IQ)	**41**	**72**
Arithmetic (Z)	**-2.4**	0.6
Stroop - colour naming (Z)	**-3.0**	-0.3
Stroop - word reading (Z)	**-3.0**	-0.3
Stroop - inhibition (Z)	**-3.0**	**-2.7**
Object decision (Z)	**-2.25**	0.0

Bold numbers indicate impaired scores (cut of point: 5th percentile ≡ Z=-1.67 ≡ IQ=75). KEY: *, test conducted 1.5 years prior to the current study; [1], calculated using the '2nd error procedure' in which raw score was the number of correct items prior to making a 2nd incorrect response; Arithmetic, Graded Difficulty Arithmetic test (Jackson and Warrington, 1986); BPVS, British Picture Vocabulary Scale (Dunn et al., 1982); Digit span, WMS-R Digit Span (Wechsler, 1987); GNT, Graded Naming Test (Warrington, 1997); MMSE, Mini Mental State Examination (Folstein et al., 1975); Object decision, test of visual object perception taken from the Visual Object and Space Perception Battery (VOSP, Warrington and James, 1991); PALPA, Psycholinguistic Assessments of Language Processing in Aphasia (Kay et al., 1992); RMT, Recognition Memory Test (Warrington, 1984); Schonell reading, Schonell graded word reading test (Schonell and Schonell, 1960); Single word repetition, 20 low frequency items with 1, 2 or 3 syllables selected from the word repetition test of McCarthy and Warrington, 1984; Spatial span, WMS-III Spatial Span (Wechsler, 1997); Stroop, D-KEFS Stroop test (Delis et al., 2001); Synonyms, (Warrington et al., 1998); WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

4.5 General non-verbal auditory assessments

A battery of tests was constructed to assess three broad and relatively dissociable stages of non-verbal auditory cognition: property, apperceptive and semantic processing. At the property processing level, tests of pitch and timbre perception were created to assess two relatively independent perceptual mechanisms (e.g., Mazzuchi et al., 1982; Peretz et al. 1994): whilst pitch is a relatively basic property associated with spectral processing, timbre is a relatively complex property associated with spectrotemporal processing. At both the apperceptive and semantic level, several independent measures were created to circumvent the bias that may be inherent in any single test, and to assess the processing of several different auditory object categories (environmental sounds, music, emotions). A summary of each test is given below, and detailed descriptions of stimuli are provided in the chapter appendix.

4.5.1 General non-verbal auditory assessments: Methods

4.5.1.1 Property processing: Pitch

To assess pitch processing, two tests comprising pure tones of either fixed or changing pitch (frequency) were created. The first test, ‘pitch detection’, consisted of pure tones with either fixed or gradually ascending pitch (sound examples 30-31); the second test, ‘pitch direction’, consisted of pure tones with either gradually ascending or descending pitch (sound examples 32-33). Subjects were asked to report whether each sound went ‘up or stayed the same’ (detection), or ‘up or down’ (direction).

4.5.1.2 Property processing: Timbre

To measure the perception of spectrotemporal information relevant to timbre, a test requiring the processing of conjoint spectral and temporal modulations was created. Stimuli were broadband noise with particular combinations of frequency and amplitude modulation (FM and AM), chosen to give the percept of continuous upward or downward motion (sound examples 34-35). Subjects were asked report whether each sound went ‘up or down’.

4.5.1.3 Property processing baseline: Isochrony

To assess compliance with the pitch and timbre task demands, a test using similar response procedures but reduced auditory perceptual demands was created. Specifically, this test required the detection of isochronous (temporally

regular) note sequences, which is a relatively basic auditory process reliant upon sub-cortical and cortical brain regions (Teki et al., 2011) commonly unaffected in PPA. Stimuli were sequences containing multiple repetitions of a single harmonic note (with fixed characteristics), separated by either regular or irregular inter-note-intervals (sound examples 36-37). Subjects were asked to listen to each sequence and indicate whether it was ‘even or uneven’.

4.5.1.4 Apperceptive processing: Degraded sounds

In vision, apperceptive processing is held to facilitate the recognition of objects under altered viewing conditions; by analogy, auditory object apperception was probed here using perceptually degraded sounds. This test has been previously described in Chapter 3 (section 3.4.3.1.4). Sounds from two natural categories (animal vocalisations and hand-tool sounds) were degraded using a digital algorithm developed by Theunissen and colleagues (Elliot and Theunissen, 2009; sound examples 38-41). This manipulation was designed to increase reliance upon apperceptive processing by minimising the semantic content of sounds. Subjects were asked to report whether each degraded sound was more like an ‘animal calling out or a tool being used’.

4.5.1.5 Apperceptive processing: Textures

To investigate auditory object recognition, a test was devised to examine the recognition of environmental sound objects that may be referred to as auditory ‘textures’ (Overath et al., 2010). Here, auditory textures were defined as environmental sounds with a spectrotemporal profile that is relatively homogeneous and temporally extensive (such as a mechanical engine idling, heavy rain, or a crowd applauding), without any discrete auditory features (not including, for example, a car horn, a sudden clap of thunder, or a person sneezing). Although this test was primarily designed as an index of semantic processing, the incorporation of auditory textures suggests that successful performance may be particularly reliant upon mechanisms of object apperception, given requirements to analyse detailed spectrotemporal structures that do not contain any discrete identifying features. As such, this test is likely to index auditory object processing at the interface between apperception and semantics. To make the test, ten different auditory textures were chosen, with the additional requirements that (i) healthy older controls would be easily able to recognise each texture, and (ii) each texture

represented a highly familiar sound object. Although these additional requirements were applied subjectively, the generally high level of performance shown by the control group (see below) suggests that they were broadly fulfilled. The auditory textures chosen were: crowd applauding, petrol engine running, glass shattering, paper being manipulated (including tearing, crumpling or rustling), continuous frictional tool sounds (including sawing, filing, sanding), water pouring into a container, tap running into a sink, rain, waves rolling, and wind blowing. The test comprised ten exemplars of each of the ten specified auditory textures. Following each sound, subjects were asked to choose the correct texture from a visual array, in which each option was displayed as a clear colour picture or photo. Controls results revealed that the four water-based textures were commonly confused, and therefore responses to water sounds were regarded correct if any of the four water textures were selected; this scoring procedure effectively reduced the number of auditory texture types in the test from ten to seven.

4.5.1.6 Apperceptive processing: Scale

A novel test was designed to probe one aspect of music apperception: tonal (scale) processing (Peretz & Coltheart, 2003; Peretz & Zatorre, 2005). Stimuli in this scale test comprised pairs of 5 note sequences, sequentially presented and interspersed by a brief silent gap (all individual notes had equal duration); within each stimulus, sequence pairs were either identical or different. Within different pairs, the first sequence comprised the initial 5 pitches of a western major scale in ascending order, whilst the second sequence was identical to the first except for a single 'wrong' note (either 1 semitone higher or lower than the corresponding note in the first sequence; sound examples 44-45). After each stimulus, subjects were asked to respond to the following question: 'were those two sequences the same or different?' To assess compliance with the working memory demands of this test, an analogous baseline 'isochrony' measure with reduced auditory processing demands was created. The particular auditory perceptual task employed was discrimination between isochronous (temporally regular) and anisochronous (temporally irregular) sequences, chosen here because it is likely to rely upon relatively basic processing mechanisms and substrates that are commonly unaffected in PPA (Teki et al., 2011). Specifically, identical pairs comprised two isochronous sequences, whilst different pairs

comprised an isochronous sequence followed by an anisochronous sequence (with varying temporal patterns); within all pairs, pitch was held constant (sound examples 42-43). This baseline isochrony test used the same test question as the scale test.

4.5.1.7 Semantic processing: Environmental sounds

To further investigate auditory object processing, a pair of tests was constructed requiring subjects to firstly categorise and secondly identify a set of environmental sounds; these tasks are likely to index, respectively, the interface of apperceptive and semantic processing, and semantic processing proper. Sounds were divided into four categories: animal vocalisations, human non-verbal sounds, object sounds, and natural sounds. A free response procedure was employed, and subjects were asked to describe each sound as accurately as possible. If words were difficult to find or produce, answers could be given by alternative means such as miming item-specific actions (e.g., for the sound of a saw, the demonstration of a typical sawing action constituted an acceptable answer, whilst a non-specific hand movement did not). Two scores were computed: the ‘semantic category’ score was the total responses specifying the correct object category, whilst the ‘semantic object’ score was the total responses specifying the correct subordinate entity.

4.5.1.8 Semantic processing: Inside and outside sounds

To further probe the semantic processing of sound objects, a test requiring the identification of sounds that normally occur either ‘indoors’ or ‘outdoors‘ was created. In general, this criterion is orthogonal to the perceptual characteristics of environmental sounds and is therefore likely to engage semantic mechanisms. However the category of animal calls represents an exception to this rule because it shows an association between perceptual and semantic properties (outdoor sounds with a high level of spectral detail), and was therefore omitted from the test. To compare semantic processing across modalities, an analogous task was created using clear colour photographs of common objects normally found inside or outside. All stimuli were carefully selected to be: (i) highly familiar, (ii) as clearly representative of the relevant object as possible; (iii) high quality recordings/photos. Subjects were asked to report whether each sound or picture normally occurs ‘inside or outside’.

4.5.1.9 Semantic processing: Emotions

The recognition of four human non-verbal vocal emotions (happiness, sadness, anger, fear) was examined using a shortened version of a previously described test (Sauter and Scott, 2007; Sauter et al., 2010). Additionally, a shortened version of an analogous task in the visual modality comprising pictures of human facial expressions was also administered (Ekman and Friesen, 1971). Subjects were asked to choose the emotion of each sound or picture from an array of the four possible responses.

4.5.1.10 General methods

Several general principles of test design and administration were applied throughout this study. Stimuli for all auditory property processing tests were digitally synthesised using previously described algorithms run under MATLAB (MathWorks^{TM}; details of synthesis algorithms are provided in the chapter appendix). With a few exceptions (indicated in relevant sections), sounds used in all apperceptive and semantic tests were taken from online sound libraries (e.g., iStockphoto.com; lists of test stimuli are given in the chapter appendix). Unless otherwise specified, tests comprised two experimental conditions with fifty percent of stimuli in each. For all tests, total stimulus numbers are shown in corresponding results tables. To administer tests, sounds were played binaurally through a notebook computer and Sennheiser HD 280 pro headphones (Sennheiser, Wedeburg, Germany), at a sound pressure level of at least 70 dB in a quiet room. All tests were conducted separately in a stereotypical order, and within each test, stimuli were administered in a fixed random order. During testing, possible responses were displayed in both verbal and simple diagrammatic form and could be selected by naming or pointing.

Table 4.2 General non-verbal auditory assessments

Test details			Case 1	Case 2	Controls		
Test	**Max.**	**Chance**	**Score**		**Grp. (N)**	**Mean (std. dev.)**	**Min.**
Property processing							
Pitch: detection	20	10	17	16	A (20)	19.9 (0.4)	19
Pitch: direction			11	16		20.0 (0.0)	20
Timbre			18	11		19.6 (0.8)	17
Isochrony (property baseline)	10	5	10	10	A (18)	10.0 (0.0)	10
Apperceptive processing							
Degraded sounds	40	20	35	39	A (20)	37.2 (2.6)	32
Scale	16	8	unable	6	C (5)	15.4 (0.9)	14
Isochrony (scale baseline)			unable	15		16.0 (0.0)	16
Semantic processing							
Auditory textures	100	14	86	62	C (5)	98.4 (1.1)	94
Env. sounds: semantic category	42	-	36	33		38.4 (1.5)	37
Env. sounds: semantic object			31	23		35.8 (1.8)	34
Inside/outside objects: auditory	40	20	35	26	A (20)	38.4 (1.1)	36
Inside/outside objects: visual			39	40	C (5)	40.0 (0.0)	40
Emotions: auditory	20	10	14	5	B (21)	17.5 (1.6)	13
Emotions: faces			16	20		18.8 (0.7)	17.5

KEY: Chance, score expected by chance alone (see text); Env. Sounds, environmental sounds test; Grp., control group; Max., maximum score; Min., minimum; std. dev, standard deviation.

4.5.2 General non-verbal auditory assessments: Results

Results from the general non-verbal auditory assessment are presented in Table 4.2. Given the lack of variability in the control sample on a subset of tests, patient results are interpreted via comparison to both the lowest control score, and the score expected by chance alone (calculated as the number of items divided by the number of possible alternative responses for each item).

Case 1 showed particular impairments in the test of pitch direction, but was relatively preserved in the tests of pitch detection and timbre; however, her flawless performance on the test of isochrony perception (property processing baseline), suggested that observed deficits were unlikely to reflect an inability to comply with task demands. Case 1 performed within the control range on one measure of auditory apperception (degraded sounds). However, Case 1 was unable to attempt the test of musical (scale) apperception, or the corresponding baseline (isochrony) measure. Finally, Case 1 showed impaired performance on all tests involving semantic object processing (auditory textures; environmental sounds; inside/outside objects; emotions), showing approximately equivalent deficits in both auditory and visual modalities.

Case 2 showed relative preservation in both pitch processing tests, but impaired performance in the timbre test; however, her flawless performance on the test of isochrony perception (property processing baseline), suggested that she was able to comply with necessary task demands. Additionally, Case 2 performed within the control range on one measure of auditory apperception (degraded sounds). However, she exhibited a deficit of musical (scale) apperception, despite preserved performance in a test of isochrony perception matched for task demands (scale processing baseline), indicating a specific auditory deficit which cannot be accounted for by executive impairments. Finally, in comparison to Case 1, Case 2 gave relatively poorer performances on all tests of auditory semantic object processing; however, she showed preserved performance on tests of visual semantic processing (visual inside/outside objects, facial emotions).

4.5.3 General non-verbal auditory assessments: Discussion

Results from the general non-verbal auditory assessments suggest distinct patterns of deficits in Cases 1 and 2. In the tests of auditory property processing, Case 1 exhibited impairments within tests of basic property (pitch) perception, apperceptive and semantic processing. However, she showed relative preservation during complex property (timbre) perception and one apperceptive test (degraded sounds), and gave superior performances compared to Case 2 in one further apperceptive measure (auditory texture test) and all auditory semantic measures. In part, this pattern of auditory deficits may be attributable to non-auditory factors. For example, Case 1 exhibited mild impairments in visual and auditory semantic tests (and analogous verbal tests in the background neuropsychological assessment), suggesting that her auditory semantic impairments may form part of a broader, albeit mild, multi-modal semantic disorder. Additionally, given that auditory processing is likely to depend upon the tracking of changes over time, Case 1's pattern of performance might be accounted for, in part, by deficits of working memory. In support of this hypothesis, Case 1 showed preserved isochrony perception during a test with relatively low executive processing requirements (property processing baseline test), but impairments during a similar test with greater working memory requirements (scale processing baseline test); these observations suggest that her previously described deficit of verbal and spatial working memory (Table 4.1) also affects processing in the non-verbal auditory modality. However, results may also indicate the specific impairment of auditory processing mechanisms: for example, a parsimonious account of Case 1 might suggest impairments of basic property perception that lead to milder deficits at apperceptive and semantic stages of processing. Taken together, Case 1 shows widespread non-verbal auditory processing deficits which may result from a combination of multi-modal semantic impairment, limited working memory capacity, and deficits of basic auditory property perception.

In the tests of auditory property processing, Case 2 exhibited impairments of complex property (timbre) perception, apperceptive and semantic processing. However, she showed preserved performance throughout all visual object processing tests, reducing the likelihood of multi-modal apperceptive and/or semantic deficits. Given the relative preservation of further cognitive abilities

relevant to non-verbal auditory processing in Case 2 (e.g., non-verbal working memory, performance IQ; Table 4.1), this evidence suggests that deficits exhibited here may reflect specific auditory impairments. Whilst separate impairments at complex property, apperceptive and semantic stages of cognition might be postulated, a more parsimonious account would suggest that her timbre perception impairment accounts for observed deficits at subsequent stages of processing. This interpretation is supported by evidence that Case 2 exhibited more pronounced object processing impairments in tests requiring the analysis of more finely grained properties (i.e., increased spectrotemporal detail). For example, she showed relatively greater deficits in the texture test (which requires discrimination between seven relatively homogeneous categories) than the degraded sounds test (which requires discrimination between only two relatively distinct categories), whilst Case 1 showed the reverse profile. Additionally, Case 2 showed a greater performance decrement than Case 1 when required to identify rather than merely categorize auditory objects (category vs. object score on the environmental sounds test). Taken together, results suggest that Case 2 may suffer a primary disorder of complex property (timbre) processing, i.e., dystimbria, which leads to secondary impairments of apperceptive and semantic object representation.

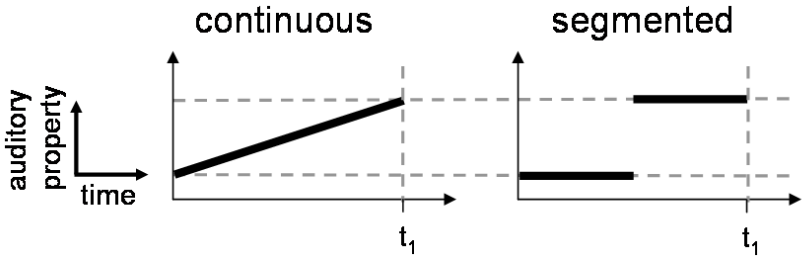
4.6 Further examination of Case 1

Above, it is argued that Case 1's performance in the general non-verbal auditory processing battery may be attributable to at least three factors: non-verbal auditory property processing deficits, limited working memory capacity, and multi-modal semantic impairments. In particular, although the tracking of temporal changes in non-verbal auditory information is likely to involve mechanisms of working memory, little is understood about the relationship between these two processes. Thus, further tests were designed to determine the relative contributions of auditory and working memory processes to the perception of basic auditory properties such as pitch and intensity in Case 1, in comparison to Case 2 and healthy age-matched controls.

4.6.1 Further examination of Case 1: Methods

Here, four tests were designed to probe the relative influences of working memory and auditory perceptual mechanisms upon auditory property change discrimination in a 2x2 factorial design. Working memory was examined by comparing the perception of 'continuous' and 'segmented' property changes (see Figure 4.2); since continuous changes provide ongoing property change information throughout the duration of a sound, they are likely to impose lower working memory demands. Additionally, mechanisms of auditory perception were examined by comparing the perception of changes in different types of properties (pitch vs. loudness). 'Segmented' stimuli comprised pairs of sequentially presented pure tones (separated by a negligible gap), featuring an auditory property 'change': here, the change was either an increase or a decrease in the relevant property (pitch or loudness) in the second sound relative to the first. 'Continuous' stimuli comprised single pure tones that continually increased or decreased in the relevant auditory property. The amount of auditory property change per unit time, or 'change salience', was systematically varied across all tests via the manipulation of three parameters: total stimulus duration, total property change, and rate of property change. Crucially however, change salience was matched as far as possible between all four tests; test stimuli are schematically depicted in Figure 4.2, further details are given in the chapter appendix, and sound examples are provided (numbers 46-53). Within each test, stimuli were administered in a fixed random order. For each test, subjects were required to report whether each sound pair went 'up or down'. Since all tests were made at a level designed to be very easy for healthy individuals, the control group completed only a sample of 10 items from each test.

Figure 4.2 Schematic diagram of stimuli used in the pitch and loudness change perception tests



Left and right hand panels depict auditory property (either pitch or loudness) changes from the continuous and segmented tests respectively; the average property change per unit time is matched between tests.

Additionally, a further analysis was planned to reveal the separate effects of the three change salience parameters upon Case 1's performance in the test of continuous pitch change perception. Although these parameters are inter-dependent, they varied widely and were uncorrelated throughout this test, thus enabling an analysis of their average effects upon performance. To permit this analysis, a large number of test items were required; therefore, the continuous pitch test was built with twice as many trials as the analogous loudness test, and Case 1 completed it on four separate occasions. Combining results from all four administrations of this test, Case 1's scores corresponding to stimuli at each level of each parameter were pooled. Performance patterns were then examined by comparing pooled results for progressively increasing values of each parameter; statistical significance was evaluated using a non-parametric trend test (Cuzick, 1985).

4.6.2 **Further examination of Case 1: Results**

Results from the four tests in this section are presented in Table 4.3. Given the near-ceiling performance of the control group, a qualitative analysis of results is presented. Throughout these tests, Case 2 showed normal levels of performance. In contrast, Case 1 showed widespread impairments for the perception of auditory property changes, irrespective of working memory load (segmented, continuous), and auditory property (pitch, loudness). However, Case 1 also showed relatively preserved performance in the test of continuous pitch change perception, compared to the other three tests.

Table 4.3 Pitch and loudness change perception: raw results

			Case 1		Case 2		Controls	
			Raw score				Scaled score: mean (std. dev.)	
Property	**Max.**	**Chance**	**Seg.**	**Cont.**	**Seg.**	**Cont.**	**Seg.**	**Cont.**
Pitch	40	20	17	31	36	38	38.4 (2.0)	40.0 (0.0)
Loudness	20	10	11	10	20	18	19.6 (0.8)	20.0 (0.0)

KEY: Cont., continuous; Max., maximum score; Scaled score, controls completed only a subset of 10 items from each test, and thus summary statistics were scaled to reflect the original size of tests; Seg., segmented; std. dev., standard deviation.

In the four repeated tests of continuous pitch perception, Case 1 scored 31, 31, 38 and 38 (in chronological order, out of a maximum of 40). Table 4.4 shows the percent of correct responses she gave for each level of each of the three parameters under investigation. Results indicate that performance improves as each parameter increases, and these trends approach statistical significance for the parameters of total pitch change (p=0.10) and rate of pitch change (p=0.10).

Table 4.4 Error rates shown by Case 1 in the continuous pitch perception test

Parameter		N	Performance (% correct)	Trend p value
Duration (s)	2.00	64	92.4	0.48
	3.00	32	97.7	
	4.00	64	97.1	
Total pitch change (Hz)	0.3	24	75.0	0.10
	0.50	24	83.3	
	0.70	24	83.3	
	0.90	24	95.8	
Rate of pitch change (Hz/s)	0.10	24	79.2	0.10
	0.17	24	87.5	
	0.23	24	87.5	
	0.30	24	95.8	

KEY: N, number of items at parameter level; Trend p value, p value from nonparametric test for trend across ordered groups, developed by Cuzick (1985).

4.6.3 Further examination of Case 1: Discussion

In this section, Case 1 showed grave impairments for the detection of changes in pitch and loudness. However, in comparison to her impairments, she showed relative preservation for the perception of continuous (as opposed to segmented) changes of pitch (as opposed to loudness). Additionally, a detailed analysis of the continuous pitch change test (Table 4.4) suggests that Case 1's performance improves with the amount of auditory property change per unit time. Given this data, several interpretations of Case 1's deficits may be offered; these alternative hypotheses will be considered in detail in the general discussion.

4.7 Further examination of Case 2

Evidence from the general non-verbal auditory battery suggested that Case 2 suffers a primary dystimbria which also affects apperceptive and semantic stages of auditory object processing. However, previous neuropsychological studies have suggested that dystimbria may be divisible into a number of distinct disorders, reflecting underlying impairments for particular spectral, temporal and/or spectrotemporal parameter ranges (Auerbach et al., 1982; Samson et al., 2002; Kohlmetz et al., 2003; Griffiths et al., 2007). Thus, two further assessments were developed here to enable a detailed description of dystimbria in Case 2. Firstly, following previous methods (e.g., Albert and Bear, 1974; Auerbach et al., 1982; Motomura et al., 1986), a test of 'click fusion' was designed to probe temporal processes particularly relevant to timbre processing and the syndrome of word deafness. Secondly, novel tests were designed to compare spectral and temporal aspects of timbre processing.

4.7.1 Further examination of Case 2: Methods

4.7.1.1 Click fusion

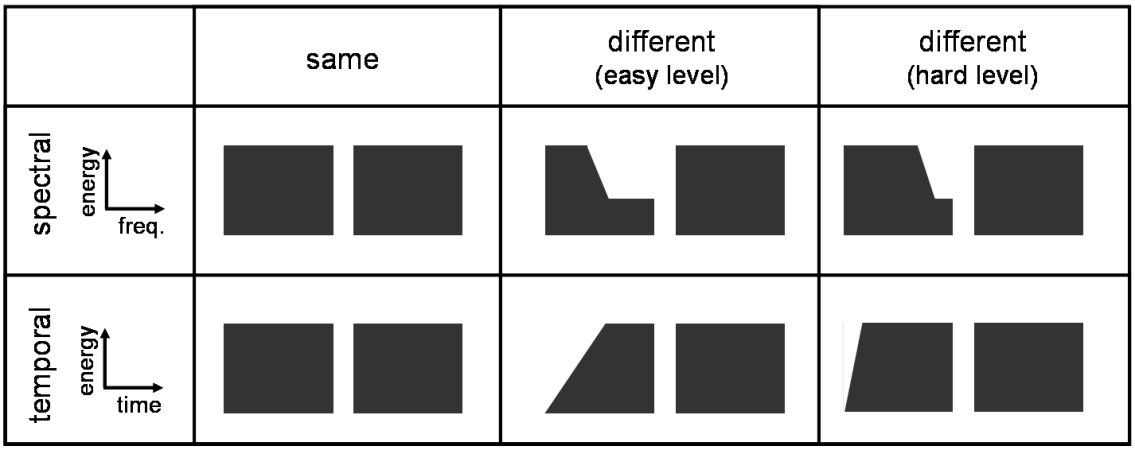
Click fusion tests index the temporal resolution of sound representations, which is one important aspect of timbre processing. Specifically, such tests are designed to determine the threshold at which a pair of noise bursts (clicks) separated by a brief inter-stimulus interval (ISI) perceptually 'fuse' into one sound. Here, analogous fusion tests in the auditory and visual modalities were created to enable the differentiation of general from auditory-specific impairments. In the auditory subtest, target trials (N=18) were composed of two sequentially presented clicks (100ms white noise bursts), interleaved by silent inter-stimulus intervals (ISI) of varying duration (18 discrete values in the range 5-400 ms). ISI durations were chosen subjectively to range in difficulty from just noticeable to easily noticeable. Non-target trials (N=18) were also created comprising a single white noise burst (200ms) without a silent ISI. Trials were administered in a fixed random order, and sound examples are provided (numbers 54-57). Subjects were required to report whether each trial contained a 'gap' or 'no gap'. An analogous test was created in the visual modality using identical temporal parameters. Here, target trials were composed of two sequentially presented rectangles interleaved by a blank ISI of varying duration,

whilst non-target trials were composed of a single rectangle without a blank ISI. Trials were administered in the same fixed random order employed in the auditory test, and subjects were required to report whether each trial contained a ‘blank’ or ’no blank’.

4.7.1.2 Spectral and temporal shape discrimination

Two analogous tests were created to compare spectral and temporal aspects of timbre processing. Auditory stimuli were spectral and temporal ‘shapes’, i.e., sounds in which timbre is defined by patterns of energy in the domains of frequency and time respectively (see section 1.3.2). In the spectral and temporal tests, trials comprised a pair of sequentially presented spectral or temporal shapes respectively (individual shape duration=1s, inter-pair silent gap=0.5s). In both tests, the second shape of each pair was held constant; however, the first shape of each pair was either identical (‘same’ trials, N=20) or different (‘different’ trials, N=38) to the second. Throughout different trials, the salience of inter-pair variation ranged from easily noticeable (level 1) to barely noticeable (level 19; further details provided in the chapter appendix). Within each test, trials were administered in a fixed random order. Test stimuli are schematically depicted in Figure 4.3, and sound examples are provided (numbers 58-69). Subjects were required to report whether sounds in each trial were the ‘same or different’.

Figure 4.3 Schematic diagram of stimuli used in spectral and temporal shape discrimination tests



Upper row panels depict the spectral shapes of sound pairs from the spectral test; lower row panels depict the temporal shapes of sound pairs from the temporal test. For both tests, the left-hand column shows ‘same’ sound pairs, whilst further columns show ‘different’ pairs involving inter-pair variations that are either easily (middle column) or barely (right hand column) noticeable. Within each individual panel, the first and second sounds of each pair are shown on the left and right hand sides respectively. KEY: freq., frequency.

4.7.2 Analysis

T-test procedures modified for the comparison of a single patient to small normative samples (Crawford and Garthwaite, 2002; Crawford and Garthwaite, 2005; www.abdn.ac.uk/~psy086/dept/SingleCaseMethodsComputerPrograms.HTM) were employed to compare Case 2's performance to the control group. Specifically, modified unpaired t-tests (Singlims.exe; Crawford and Garthwaite, 2002) were used to examine performances within each individual test, whilst a modified paired t-test (RSDT.exe; Crawford and Garthwaite, 2005) was used to evaluate performance discrepancies between the spectral and temporal shape discrimination tests.

4.7.3 Further examination of Case 2: Results

4.7.3.1 Click fusion

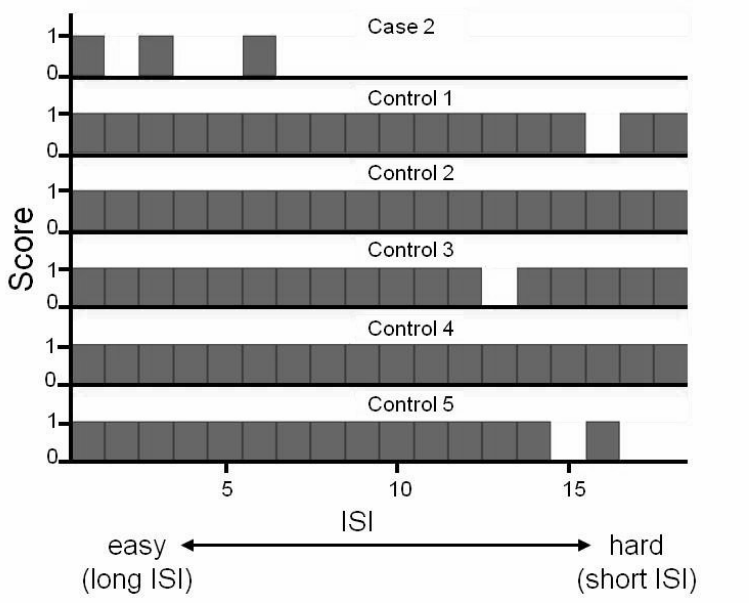
In the visual modality, all subjects including Case 2 performed flawlessly. In the auditory modality, raw results indicate that Case 2 scored far below the control range (Table 4.5), although her performance improved for stimuli with the longest ISI durations (Figure 4.4). A modified t-test (two-tailed) suggested that the difference in total score between Case 2 and the control group was statistically significant ($p<0.001$). Whilst this experiment does not permit calculation of a perceptual threshold, Case 2 showed fusion in all trials in level 7 and above, which is equivalent to ISI<85ms; notably, this result overlaps with timescales relevant to speech perception (e.g., transients <10ms, formant transitions 10-100ms).

Table 4.5 Click fusion: raw scores by subject

Subtest	Auditory	Visual
	Score /36	
Case 2	21	36
Control 1	35	36
Control 2	35	36
Control 3	35	36
Control 4	36	36
Control 5	33	36

KEY: C1-5, controls 1-5 from control group C.

Figure 4.4 Click fusion: raw results by ISI and subject



For graphical display purposes, it was necessary to transform the widely varying values of ISI into discrete difficulty levels on a linear scale; levels 1 and 18 indicated the smallest and largest gap lengths respectively. Results corresponding to stimuli with no gap are not shown. KEY: ISI, inter-stimulus interval.

4.7.3.2 Spectral and temporal shape discrimination

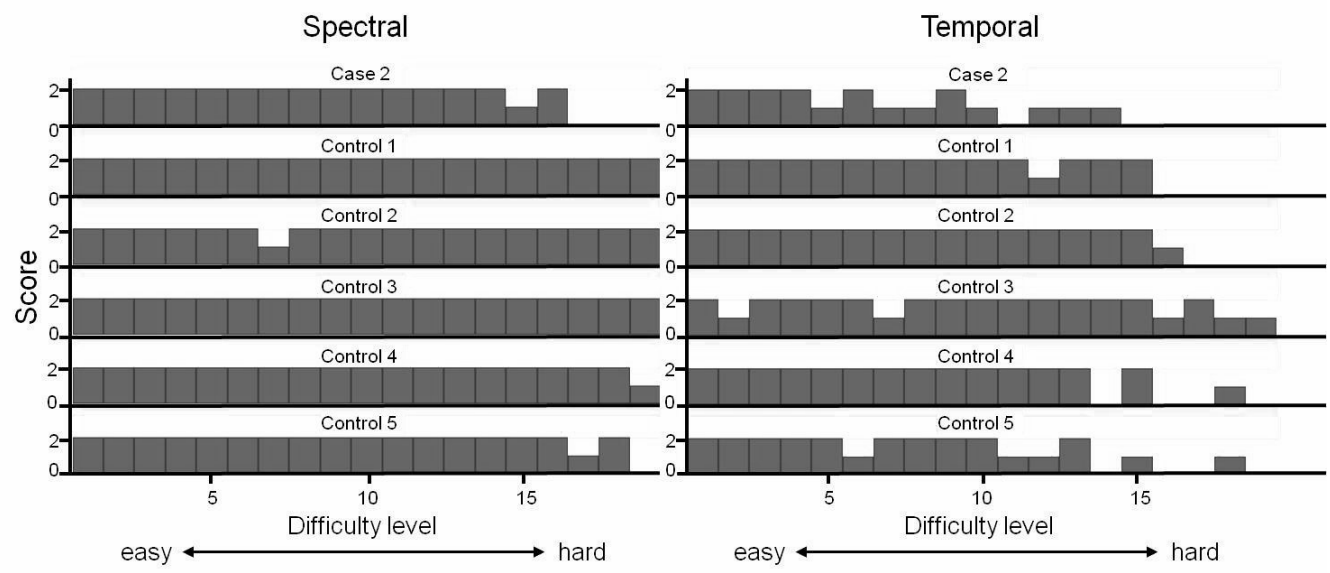
Raw scores (Table 4.6) and data plots (Figure 4.5; 'different' trials only) indicate that Case 2 performed below the control range on each test, but with relatively greater impairments on the temporal test. Additionally, data plots suggest that Case 2's performance dropped in both tests with increasing difficulty level, and that she showed particular impairments compared to controls for the easier items of the temporal test. Modified t-tests (two-tailed) suggested that the difference in total score between Case 2 and the control group was statistically significant for each test separately ($p<0.05$); however, a modified paired t-test indicated that Case 2's overall performance was equivalent in the spectral and temporal tests ($p=0.18$).

Table 4.6 Spectral and temporal shape discrimination: raw scores by test and subject

Test	Temporal	Spectral
Subject	**score /58**	
Case 2	39	51
C1	49	58
C2	51	57
C3	53	55
C4	49	57
C5	45	55

KEY: C1-5, controls 1-5 from control group C.

Figure 4.5 Spectral and temporal shape discrimination: raw scores by test, difficulty level, and subject



N.B. Only scores corresponding to 'different' sound pairs are shown.

4.7.4 Further examination of Case 2: Discussion

Results from the click fusion test indicated that Case 2 suffers a modality-specific deficit of auditory temporal resolution. Results from the auditory shape discrimination tests indicated deficits of both temporal and spectral timbre processing, although there was a trend towards greater impairments during temporal processing. Together, these findings suggest that Case 2 suffers a dystimbria involving impairments of both spectral and temporal processing, but

with particularly prominent temporal deficits. Such evidence may account for the prominence of Case 2's symptoms of word deafness: the approximate range of her temporal impairment encompasses timeframes relevant to verbal perception, and words typically make more demands upon temporal processing than other sound categories. However, present results also suggest that Case 2's spectral and temporal deficits may affect auditory property processes necessary for the perception of many different natural sound categories (Woolley et al., 2005). Therefore, to the extent that property processing disorders give rise to secondary deficits at subsequent stages of cognition, the results of this section may also account for Case 2's widespread auditory object processing impairments at both apperceptive and semantic levels.

4.8 General discussion

This study presents a detailed neuropsychological assessment of two patients with distinct syndromes of primary progressive aphasia (PPA) and distinct profiles of non-verbal auditory impairment. Case 1 fulfilled criteria for the syndrome of logopenic progressive aphasia (LPA) and exhibited impaired perception of basic auditory properties (pitch, loudness) and a deficit of non-verbal auditory working memory, with relatively preserved perception of a more complex auditory property (timbre). In contrast, Case 2 fulfilled criteria for the syndrome of progressive non-fluent aphasia (PNFA) and showed a relatively selective deficit of timbre perception (dystimbria) with relatively preserved perception of more basic auditory properties (pitch, loudness). In addition, whilst Case 1 showed relatively mild deficits of auditory object (apperceptive and semantic) cognition, object-level deficits in Case 2 were generally more severe (although the reverse pattern was found in object tests with significant working memory requirements). However, both patients performed within the control range on one measure of auditory apperception (degraded sounds), suggesting that certain auditory apperceptive mechanisms can operate normally even when the processing of particular auditory properties is impoverished. Taken together, these cases provide evidence for a double dissociation between processing basic and more complex auditory properties, thus indicating that certain stages of auditory object property processing may proceed in parallel to one another. Further, they may suggest a particular reliance of basic perceptual property

processing mechanisms upon working memory resources. Additionally, results indicate that certain property processing deficits (such as dystimbria) disrupt object-level computational stages whereas others leave such processes largely intact. This particular conclusion provides evidence for a serial information flow between complex property (timbre) and object-level representations; indeed, unlike more basic property processes (pitch, loudness), timbre is a key component of auditory object identity and is likely to be critical for auditory object discrimination and recognition. Further, this formulation is consistent with previous evidence for the predominantly serial processing of increasingly complex stages of non-verbal auditory cognition, collected in both human and animal populations (Rauschecker, 1998; Binder et al., 2000; Wessinger et al., 2001; Griffiths and Warren, 2004). Although detailed anatomical correlation was not possible in the present cases, current data provides some evidence that particular auditory property processing stages have distinct anatomical substrates: whilst both patients exhibited predominantly left-sided peri-Sylvian atrophy, there was greater involvement of the temporo-parietal junction in Case 1 and more anterior superior temporal regions in Case 2 (Figure 4.1). Taken together, the examination of Cases 1 and 2 both adds to the literature of non-verbal auditory processing deficits in PPA, and enhances the understanding of corresponding cortical mechanisms in the healthy brain. The remaining discussion comprises a detailed discussion of each case separately, followed by a consideration of the limitations and implications of the current study.

4.8.1 Case 1

Case 1 showed grave impairments of basic auditory property processing, particularly affecting detection of changes in pitch and loudness, but normal timbre perception. However, Case 1 exhibited relatively preserved perception of continuous (in contrast to segmented) pitch changes, whereas no similar advantage was evident for perception of continuous loudness changes. Despite these deficits, Case 1 showed only mild impairments of apperceptive and semantic processing of auditory objects (excluding the music apperception tests, in which her poor performance may be explained by additional working memory deficits). Given this data, at least three alternative interpretations of Case 1's deficits may be offered. Firstly, a 'basic perceptual' interpretation might postulate the selective preservation of mechanisms for encoding dynamic (as

opposed to static) pitch information in the context of a general impairment of non-verbal auditory property perception. Secondly, a 'multiple deficit' interpretation might suggest separate impairments of non-verbal auditory property perception, memory, and attention; furthermore, the interaction of such impairments might exhibit a degree of property-specificity, thus accounting for the relative preservation of continuous pitch change discrimination. Finally, Case 1 may suffer damage to a core sub-process of auditory scene analysis (ASA), specifically involving the matching of incoming sounds to stored representations or 'auditory templates'; notably, this particular computation is likely to constitute a key stage of auditory object processing. These alternative hypotheses will now be discussed.

Firstly, a range of evidence suggests that the continuous (dynamic) changes of pitch assessed in this study, which comprised a basic form of frequency modulation (FM), are encoded as a primary property of sound by dedicated cortical processors. For example, FM is likely to provide key information for the perception of many behaviourally important sounds such as speech (Woolley et al., 2005; Singh and Theunissen, 2003; Elliott and Theunissen, 2009). Additionally, pitch glide perception is associated with behavioural advantages in psychoacoustic studies of humans (Dooley and Moore, 1988; Sek and Moore, 1999; Lyzenga et al., 2004; Demany et al., 2009), as well as selective responses in single neurons within animal auditory cortices (e.g., Whitfield and Evans, 1965; Zhang et al., 2003). Therefore, a 'basic perceptual' interpretation of current data may suggest that Case 1 shows relatively selective preservation during FM perception, thus indicating the relative cognitive independence of corresponding mechanisms in the healthy brain. Further, atrophy within the auditory cortices was observed in Case 1 and might provide an anatomical basis for this pattern of performance.

Whilst a 'basic perceptual' account of results is theoretically possible, observations in Case 1 of widespread cortical damage and cognitive deficits alternatively suggest a more complex account of results. Specifically, a 'multiple deficit' interpretation of data might suggest separate impairments of non-verbal auditory property perception and executive processes such as working memory and attention. For example, Case 1 may suffer a general deficit of auditory

property perception which is partially alleviated for pitch processing (whether involving dynamic or static information), and a general deficit of working memory for non-verbal sounds which is partially alleviated when memory load is reduced (i.e., during the perception of continual as opposed to segmented property changes); moreover, current data suggest an interaction between these deficits, such that performance is preserved only during the discrimination of pitch changes that impose low memory loads. Notably, this interpretation indicates the relatively selective impairment, and thus relative cognitive independence, of pitch processing mechanisms. This particular conclusion is supported by previous neuropsychological reports of patients with selective pitch perception impairments (Lechevalier et al., 1984; Tanaka et al., 1987; Zatorre, 1988; Tramo et al., 2002; Terao et al., 2005), as well as neuroimaging studies of healthy subjects which implicate circumscribed cortical regions (secondary auditory cortex) in pitch processing (Patterson et al., 2002; Gutschalk et al., 2004; Penagos et al., 2004; Schneider et al., 2005). Additionally, a 'multiple deficit' interpretation of data indicates the separate involvement of working memory mechanisms, and this notion gains support from several lines of evidence. Firstly, a priori inference suggests that working memory is likely to hold particular relevance to auditory perception given the requirement to track the evolution of sounds over time. Additionally, individuals with the developmental disorder of congenital amusia show relatively specific deficits for pitch perception which are, in part, attributable to working memory impairments (Tillmann et al., 2009; Liu et al., 2010; Williamson et al., 2010). Moreover, both current and previous evidence (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2011; Rohrer et al., 2010c) suggest that patients with LPA are likely to suffer predominant working memory deficits. Further, previous neuroimaging studies indicate at least a partial sharing of working memory resources between modalities (Klemen et al., 2009; Koelsch et al., 2009; Protzner et al., 2009; Schulze et al., 2010), suggesting that established verbal and spatial working memory impairments in LPA (Gorno-Tempini et al., 2008) may form part of a wider disorder that also affects non-verbal auditory processing. Here, the discrepancy in Case 1 between performance in separate measures of isochrony perception with varying task demands (property vs. scale baseline tests), suggests a specific impairment of non-verbal auditory working memory. A 'multiple deficit' account of Case 1 might also suggest the

involvement of executive functions beyond working memory, including attention to guide the allocation of cognitive resources and long term memory to support the explicit recognition of properties; indeed, Case 1 showed both executive and long term memory deficits. Together, these arguments may suggest that Case 1 suffers a combination of auditory perceptual and executive (memory, attention) impairments; additionally these deficits may interact in a property-specific manner, resulting in the selective preservation of continuous pitch discrimination. Although a degree of independence between these postulated perceptual and executive deficits may be suggested, their interaction might also indicate damage to a unified neural network incorporating both types of process. This conclusion is supported by previous neuroimaging studies of healthy controls and subjects with congenital amusia, which describe distributed auditory processing networks linking regions associated with both perceptual and executive mechanisms, and furthermore show a degree of functional specialisation for pitch (e.g., Schulze et al., 2010; Schulze et al., 2011; Hyde et al., 2006; Hyde et al., 2007; Peretz et al., 2009; Hyde et al., 2010). Indeed, Case 1 showed atrophy within temporal and inferior parietal regions implicated in these networks and previous evidence indicates that PPA leads to network-level cortical damage (Seeley et al., 2009). Thus, current evidence may suggest that Case 1 suffers multiple separable but closely associated perceptual and executive deficits, following damage to a functionally coherent auditory property processing network.

However, a third and more parsimonious account of Case 1 might suggest a unitary defect of auditory processing which differentially affects the perception of particular types of properties (pitch, loudness, timbre) and objects (continuous, segmented) according to the computational load that they impose. In particular, auditory processing depends upon a core mechanism of auditory scene analysis (ASA) to facilitate the segregation of sound mixtures into constituent objects prior to the subsequent processing of sound identity (Bregman, 1990; see section 1.5.4.1). ASA is likely to depend upon multiple sub-processes including the ‘bottom-up’ analysis of basic perceptual properties in the sound mixture, and the ‘top-down’ application of stored auditory perceptual knowledge. Specifically, ‘top-down’ processes may entail the matching of incoming sound mixtures to stored ‘auditory templates’, which are

held to specify the perceptual characteristics of sound objects based on past auditory experience (Bregman, 1990; Griffiths and Warren, 2002; Warren et al., 2005b). Whilst bottom-up processes are likely to proceed relatively automatically, demands upon top-down template matching processes are likely to vary with the types of properties and objects contained in a sound mixture. For example, the multidimensional property of timbre is closely linked to sound identity, and may therefore form a key component of auditory templates. On the other hand, pitch is a less specific identity cue, since pitch variations commonly occur within single auditory objects (e.g., animal vocalisations). However, pitch patterns are fundamental building blocks of auditory objects and distinguish natural sound categories (Woolley et al., 2005; Singh and Theunissen, 2003; Elliott and Theunissen, 2009); furthermore, discontinuities in pitch provide important cues for object segregation (e.g., Bregman, 1990; Deike et al., 2010; Goll et al., 2010). In contrast, the property of loudness shows large within-object variation, and as a consequence, sound recognition often depends upon a capacity to adjust for loudness information (Billimoria et al., 2008). Thus, the computational load imposed by different auditory properties upon the template-matching mechanism is likely to vary: multidimensional and object-specific timbre cues may facilitate successful 'template matches', pitch cues may be matched more efficiently if they map onto single objects, and loudness cues are unlikely to contribute to a successful match. Furthermore, this putative matching process will depend upon the tracking of sounds as they evolve over time, and is therefore likely to integrally involve working memory resources. Thus, it might be proposed that complex auditory mixtures containing multiple objects and discontinuities are likely to tax the template-matching process more than single and relatively continuous sounds. Here, Case 1 showed a severe impairment of loudness change perception, a more restricted impairment of pitch change perception particularly affecting multi-object (segmented) stimuli, and normal timbre perception. As such, her performance varied with both the type of properties and the number of objects in the auditory 'scene', and thus may reflect an underlying deficit of auditory template matching.

It is likely a priori that the putative template matching algorithm and its top-down inputs would be instantiated at the level of a neural network; indeed, this is consistent with previous neuroimaging and neuropsychological evidence. ASA

is likely to depend upon a distributed frontotemporal network including key substrates in the posterior superior temporal lobe and in particular the planum temporale (Deike et al., 2004; Deike et al., 2010; Smith et al., 2010; Overath et al., 2009; Schönwiesner et al., 2007), while a network of temporal, inferior parietal and frontal regions linked via the dorsal auditory cortical pathway has been implicated in pitch change processing and working memory for pitch (Schulze et al., 2010; Schulze et al., 2011; Hyde et al., 2006; Hyde et al., 2007; Peretz et al., 2009; Hyde et al., 2010). Here, atrophy in Case 1 involved the dorsal auditory pathway including the planum temporale and temporo-parietal junction, providing a candidate substrate for the proposed deficit of auditory template matching.

The preceding discussion has emphasised that a precise characterisation of Case 1's cognitive deficits cannot be offered on the basis of present findings. Nonetheless, an appeal to parsimony, together with previous evidence that PPA involves damage to functionally coherent large-scale brain networks (Seeley et al., 2009), may favour the 'auditory template' account of results. Whichever hypothesis is correct, this study reveals that dementia modulates brain mechanisms of auditory processing in a distinctive, disease-specific fashion. Such observations suggest that further group studies of similar patients (and healthy controls), using methods to correlate behavioural and neuroimaging data, may provide important insights into both the nature of auditory deficits in PPA and the organisation of auditory processing mechanisms in the healthy brain.

4.8.2 Case 2

Case 2 presented with relatively selective impairments in the comprehension of auditory objects and particularly speech, despite relatively preserved comprehension in other modalities (e.g., for written and visual material); on clinical grounds, her syndrome could therefore be described as word deafness (Auerbach et al., 1982). In the current experimental auditory tests, Case 2 showed impairments for processing complex spectral, temporal and spectrotemporal properties that are likely to be relevant to the formation of object representations, despite preserved perception of more basic spectral and temporal properties (pitch, loudness). Previous evidence suggests at least two

distinct subtypes of word deafness (see section 1.5.3.3). Rarely, cases show predominantly apperceptive deficits that are relatively selective for the category of words: such cases tend to be associated with left-sided damage to auditory association cortex (superior temporal gyrus; Wang et al., 2000; Stefanatos et al., 2005). However, the majority of word deafness cases exhibit temporal processing deficits which affect multiple sound categories but disproportionately degrade the perception of rapid transitions in speech: these cases typically have bilateral damage involving primary auditory cortex or its sub-cortical connections (although anatomical substrates vary; Albert and Bear, 1974; Auerbach et al., 1982; Miceli, 1982; Tanaka et al., 1987; Yaqub et al., 1988; Buchtel and Stewart, 1989; Otsuki et al., 1998). Here, a detailed psychoacoustic examination of Case 2 revealed deficits of complex spectral and temporal property processing, but with a particularly severe impairment of temporal property processing. The additional deficits of spectral processing exhibited by Case 2 have not been emphasised in previous reports of word deafness, but may hold a clue to the nature of the syndrome. In particular, these findings indicate that (alongside the majority of previous word deafness patients) Case 2 has a disproportionate deficit in the fine-grained analysis of temporal changes; however, they further suggest that this deficit is part of a dystimbria syndrome affecting the representation of spectral, temporal and spectrotemporal information relevant to the formation of object representations. Further reports of dystimbria (without word deafness) suggest that this disorder is heterogeneous: previous cases have shown predominant spectral (Griffiths et al., 2007) or spectrotemporal (Kohlmetz et al., 2003) deficits in association with right-sided damage to the auditory cortices. Moreover, a neural basis for the heterogeneity of dystimbria is provided by neuroimaging studies of healthy controls, which describe a distributed topographical organization of property processing mechanisms throughout auditory cortices. Specifically, spectral and temporal sub-processes may be lateralised to the right and left hemispheres respectively (Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010), whilst spectrotemporal representation is likely to occur within posterior auditory association cortices (Altmann et al., 2010). Additionally, further studies suggest that timbre analysis is likely to rely upon the concerted operation of these processes within a functionally unified superior temporal lobe network (Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010;

Kumar et al., 2007; Griffiths et al., 2007). Here, Case 2 showed bilateral but predominantly left-sided frontotemporal atrophy with particular involvement of the left superior temporal lobe; on the basis of the neuroimaging evidence outlined above, this pattern may account for the predominance of temporal over spectral deficits. Taken together, current evidence may suggest that at least some cases of word deafness represent a dystimbria with predominantly temporal characteristics, arising in association with damage to auditory cortices in the left hemisphere. Further, the observation of dystimbria in a neurodegenerative disease that involves selective damage to functionally coherent brain regions (Seeley et al., 2009) provides further evidence that timbre processing is reliant upon network-level operations within the superior temporal lobes; however, the anatomy of this network is not revealed by current data.

4.8.3 Limitations of the current study

The current study is subject to a number of methodological limitations. Firstly, both Cases 1 and 2 exhibited widespread cognitive impairments and anatomical damage, leaving open the possibility that their auditory deficits are at least partially attributable to the non-specific effects of neural degeneration. However, such factors would be unlikely to account for the patterns of relative preservation and impairment observed, although future studies involving patient groups ranging in disease severity and in a range of clinical neurodegenerative syndromes will be required to resolve this issue. Additionally, condition-specific effects observed within three of the current test sets (change perception, click fusion, shape discrimination) may partially reflect incomplete matching of certain experimental factors. Firstly, perceptual salience may have varied between the pitch and intensity change perception tests, and between the spectral and temporal shape discrimination tests; however, the use of a wide range of difficultly levels for all properties (including exceptionally easy items) suggests at least a broad overlap between conditions within each test set, although future research might seek to determine psychoacoustic thresholds in controls. Secondly, modality-specific effects (e.g., Soto-Faraco and Spence, 2002) suggest a discrepancy between the temporal processing requirements of the auditory and visual click fusion tests; however, the flawless performance of Case 2 in the visual modality nonetheless suggests that deficits in the auditory

modality are unrelated to task compliance factors. Further, the reliance upon qualitative comparisons between patients and controls within sections of this study, imposed by a lack of variance in control samples, recommends a cautious interpretation of results; future studies might tackle this problem via the use of more sensitive tests with larger item numbers and more finely-graded difficulty levels. Finally, single case studies, though informative, must in general await elaboration in complementary group studies that are powered to quantify deficits in relation to other cognitive and disease factors.

4.8.4 Implications of the current study

Current results add weight to the neuropsychological literature of selective deficits of auditory processing in PPA (Confavreux et al., 1992; Otsuki et al., 1998; Kuramoto et al., 2002; Uttner et al., 2006; Iizuka et al., 2007; Jorgens et al., 2008; Chapters 2 and 3), and therefore have implications for the clinical management of patients. For example, the demonstration of incapacitating non-verbal auditory deficits in both LPA and PNFA indicates a need to develop processes for the recognition and management of such symptoms in dementia care settings. Although it is unlikely that non-verbal auditory processing disorders would benefit from specific auditory treatments (such as amplification via hearing aids), it is possible that symptoms might be managed by increased awareness and modification of the acoustic environment.

From a cognitive perspective, the present findings suggest that non-verbal auditory cognition consists of several relatively independent mechanisms which nevertheless exhibit important interactions with other processes. Moreover, the deficits described here indicate that auditory cognition is likely to involve process-specific neural networks; in particular, Case 1 may demonstrate damage to a putative frontotemporal network for auditory template matching, whilst Case 2 exhibited involvement of a superior temporal network previously implicated in complex perceptual property (timbre) processing. Notably, these findings are compatible with recent evidence that neurodegenerative disease involves selective damage to functionally coherent neural networks (Seeley et al., 2009). If this interpretation is correct, it would follow that network-specific dysfunction in PPA can produce coherent syndromes of non-verbal auditory as well as verbal impairment. Moreover, the relative specificity of the deficits

exhibited by these two patients may imply a relative independence between mechanisms of auditory template and timbre processing in the healthy brain. Future studies combining cognitive and anatomical methodologies will be required to establish more fully the nature of non-verbal auditory processing deficits in PPA and other neurodegenerative syndromes, and to define the organisation of corresponding neural mechanisms in the healthy brain.

4.9 Chapter appendix

Table 4.7 Control group details

Group	N	Sex (M:F)	Age (years)	Education (years)	Formal music training (years)	Verbal IQ	Perf. IQ
			Mean (Std. Dev.)				
A	20	6:14	65.1 (7.7)	13.6 (3.6)	5.8 (13.3)	120.6 (6.6)	-
B	21	11:10	67.0 (8.8)	12.7 (3.7)*	-	-	116.5 (8.7)**
C	5	5:0	67.2 (4.6)	11.4 (1.7)	0.7 (0.8)	110.4 (5.9)	121.0 (6.5)
D	5	2:3	33.8 (7.9)	15.6 (3.0)	0.2 (0.4)	-	-

KEY: M, male; F, female; Std. Dev., standard deviation; Perf. IQ, performance IQ.; *, based on N=18; **, based on N=20.

4.9.1 Stimuli details

Property processing: Pitch

Pure tones stimuli (all duration=2s) were synthesized digitally in MATLAB (MathWorks^{TM}) using a custom-built script. All tones either had fixed, descending, or ascending frequency (pitch). All ascending and descending tones had a pitch excursion between 0.6-0.8 octaves, and a rate of pitch change between 0.3-0.4 octaves per second. Values of centre pitch (range: 230-270 Hz) and absolute intensity varied throughout the test.

Property processing: Timbre

Stimuli were synthesised using a previously described algorithm (Chi et al., 1999), run under MATLAB (MathWorks^{TM}). Two particular combinations of frequency modulation and intensity (temporal) modulation were used to produce clear upward and downward sweeps: (i) 2 cycles/octave, 5 Hz; (ii) 2.5 cycles/octave, 6 Hz. Values of centre pitch (range: 230-270 Hz) and absolute intensity varied throughout the test.

Property processing: Baseline

Sound sequences were formed via the repetition of a single harmonic sound (duration 60ms, pitch 423Hz, flat temporal and spectral envelope, fixed frequency bandwidth 2950 Hz), synthesized using a previously described algorithm (Warren et al., 2005a) run under MATLAB (MathWorks^{TM}). In regular

sequences, inter-note intervals were held constant (135ms), whilst in irregular sequences they were varied (21-930ms). Throughout the test, sequence duration (12s) was held constant whilst absolute intensity was varied.

Apperceptive processing: Music

Stimuli were digitally synthesised using Finale® music notation software (www.finalemusic.com). In the scale test, the starting note of the major scale varied between stimuli, and all notes had equal duration. In the baseline (isochrony) test, pitch was held constant within each stimulus, but varied between stimuli. Throughout both tests, stimulus duration (7s) and absolute intensity were held constant.

Semantic processing: Environmental sounds

Across the set of sounds, duration varied between 2.3 and 13.8s (mean=6.8s, standard deviation=2.3s), and intensity was fixed. Stimuli are detailed in Table 4.8.

Table 4.8 Auditory objects used in the environmental sounds test

Animal calls	Cat meowing 1	**Objects**	Chopping with kitchen knife 1
	Cat meowing 2		Chopping with kitchen knife 2
	Cow moos		Cutlery clattering together
	Dog barking		Engine running 1
	Duck calling		Engine running 2
	Hen clucking		Glass breaking 1
			Glass breaking 2
	Horse neighing		Hammering
			Paper - crumpling
	Sheep baas		Paper - turning pages
			Pouring liquid into container 1
Non-verbal human	Man coughing		Pouring liquid into container 2
	Crowd applauding, no cheering 1		Sawing 1
	Crowd applauding, no cheering 2		Sawing 2
	Man laughing 1		Scissors
	Man laughing 2		Stapler
	Man snoring		Tap running into sink 1
	Man whistling		Tap running into sink 2
	Man yawning	**Natural phenomena**	Ocean waves 1
			Ocean waves 2
	Woman laughing		Rain 1
			Rain 2
	Woman sneezing		Wind 1
			Wind 2

Numbered items indicate distinct exemplars of the same sound source.

Table 4.9 Auditory and visual stimuli used in the inside/outside tests

Auditory	Visual	Auditory	Visual
Inside		**Outside**	
brushing teeth with a toothbrush	Thimble	boat horn sounding	traffic lights
chopping food with a knife 1	kitchen knife	car horn sounding	hosepipe
chopping food with a knife 2	tea cup and saucer	car starting	car
cuckoo clock sounding	clock	chainsaw being used	chainsaw
electronic clock alarm sounding	electric fan	chopping a tree down with an axe	axe
footsteps on wooden floor	piano	emergency vehicle siren sounding	ambulance
gurgling from a kitchen sink	sofa	fireworks	wooden bench
kitchen cutlery clattering together	stainless steel fork	footsteps in grass	pebbles
kitchen plates clattering together	dinner plate	footsteps on gravel	campfire
manual typewriter being used	computer	helicopter engine running	bicycle
scissors cutting paper	scissors	horse galloping	leaf
stapler being used	toaster	lawnmower engine running	lawnmower
stirring in a cup with a spoon	kettle	lawnmower starting	van
tap running into a sink	bed	pickaxe bring used	trowel
tapping a cup with a spoon	wooden spoon	rain on a pavement	waves 2
telephone ringing	telephone	raking dirt	rake
toilet flushing	roll of toilet paper	scraping shovel on icy driveway	public telephone box
vacuum cleaner	vacuum cleaner	shovelling gravel	shovel
washing machine spinning	washing machine	train horn sounding	tractor
whisking in a bowl	saucepan	waves lapping on a shore	waves 1

Numbered items indicate distinct exemplars of the same sound source.

Semantic processing: Inside and outside sounds

Stimuli were matched as closely as possible between the auditory and visual modalities. Across the set of sounds, duration varied between 2.4 and 21.8s, and intensity was fixed. Whilst picture dimensions varied, all were shown in an enlarged size (ranging from ~300x400 to ~800x800 pixels) on a 19" notebook computer screen, and subjects were allowed to view each photo for as long as required. Stimuli are detailed in Table 4.9.

Pitch and loudness change perception

Stimuli were synthesized digitally in MATLAB (MathWorks^{TM}) using a custom-built script. Since appropriate psychometric functions were unavailable, values of change salience were sampled at evenly spaced intervals across a very wide parameter range (in order to vary difficulty and include items that would be extremely easy to perceive), and subjectively matched between pitch and intensity tests. Stimulus values are detailed in Table 4.10.

Table 4.10 Pitch and intensity change perception: stimuli parameters

Auditory property	Property change salience parameter values (range)		
	Total stimulus duration	Total property change	Rate of property change
Pitch	2 - 4 s	0.2 - 1.2 oct	0.075 - 0.45 oct/s
Loudness	2 - 4 s	8 - 10 dB	2 - 4.5 dB/s

KEY: dB, decibels; oct, octave; s, seconds.

Click fusion

In the auditory test, sounds were Gaussian white noise centred on 2kHz, and absolute intensity was held constant. Sounds were synthesized using a previously described algorithm (Warren et al., 2005a) run under MATLAB (MathWorks^{TM}). In the visual test, bright green rectangles of constant size (149x120 pixels) were synthesized using a digital image manipulation programme (GIMP, www.gimp.org). Rectangles were presented against a black background on a 19" notebook computer screen.

Spectral and temporal shape discrimination

Sounds were synthesized using a previously described algorithm (Warren et al., 2005a) run under (MathWorks^{TM}). The second sound of each pair in each test (the 'baseline' sound) had the following characteristics: bandwidth 0-1.5kHz, fundamental frequency 240Hz, rise and fall time 10ms. To create the first sound of each pair in the spectral test, the power of the baseline sound was reduced by a constant amount within varying frequency ranges; the upper limit of the reduced power range was held constant at 1.5kHz, whilst the lower limit varied within the range 0.3-1.2 kHz, taking 19 equally-spaced values. To create the first sound of each pair in the temporal test, the rise time varied within the range 50-950 ms, taking 19 equally-spaced values. Since appropriate psychometric functions were unavailable, shape parameters were sampled across a wide range and subjectively matched between spectral and temporal tests. Throughout both tests, absolute intensity was varied. Within spectral shape pairs, absolute intensity was held constant, whilst within temporal shape pairs, absolute intensity was matched as closely as possible (by equating intensity after the rise time).

5 Altered brain mechanisms of non-verbal sound analysis in Semantic Dementia

5.1 Summary

Semantic dementia (SD) is a unique neurodegenerative syndrome involving the selective and progressive pan-modal deterioration of semantic knowledge; SD therefore provides an ideal disease model in which to study brain mechanisms of auditory semantic processing. In this study, fMRI was used to investigate BOLD responses to auditory objects in 9 patients with SD, in comparison to 22 healthy controls. Patients showed differential activation of cortical areas surrounding the superior temporal sulcus (STS) both for perceptual processing of spectrotemporally complex but meaningless sounds, and semantic processing of sound category (animal versus tool sounds). Findings suggest that SD is underpinned by defective brain mechanisms of auditory object processing spanning pre-semantic perceptual and semantic category formation. This disease model suggests that antero-lateral temporal cortical mechanisms are critical for representing and differentiating semantic sound categories.

5.2 Background

The literature of non-verbal auditory semantic processing has been reviewed in detail in the introduction (section 1.5.5); however, a brief summary is provided here to highlight concepts relevant to the current study.

Semantic processing, or object recognition, is held to involve both 'multi-modal' semantic representations, involving information coded within one or more particular modalities (e.g., Warrington and McCarthy, 1987; Damasio, 1989; Tranel et al., 1997; Caramazza and Shelton, 1998; Crutch and Warrington, 2003; Barsalou et al., 2003), and amodal semantic representations, involving information coded in abstract form (Devlin et al., 1998; Tyler and Moss, 2001; Rogers and McClelland, 2004). Whilst the majority of object recognition studies have been conducted using visual and verbal stimuli, a growing body of literature suggests that similar cognitive representations are involved during analogous processes in the auditory modality (Bozeat et al., 2000; Lewis et al,. 2005; Leaver and Rauschecker, 2010).

Evidence for the influence of amodal semantic representations upon auditory object recognition has been derived via the study of patients with semantic dementia (SD). SD involves the highly selective degeneration of semantic knowledge in all modalities tested, without corresponding perceptual impairments; thus, deficits are most parsimoniously accounted for by an impairment of amodal semantic processing (Bozeat et al., 2000; Bozeat et al., 2002; Coccia et al., 2004; Luzzi et al., 2007). Further, since SD is associated with selective atrophy to a functionally coherent cortical network centred upon the anterior temporal lobes (ATLs; Gorno-Tempini et al., 2004; Schroeter et al., 2007; Rohrer et al., 2009; Seeley et al., 2009; Rohrer et al., 2010b), a substrate for amodal semantic processing mechanisms is suggested, and convergent anatomical evidence is provided by repetitive trans-cranial magnetic stimulation (rTMS) studies of healthy controls (Pobric et al., 2007; Pobric et al., 2010b; Visser et al., 2010b). Additionally, although SD is predominantly associated with amodal semantic processing impairments, recent evidence indicates that performance may vary between fine-grained object categories, suggesting additional deficits of multi-modal semantic processing (e.g., patients show

greater impairments for colour than shape words, and for face-movement than leg-movement words; Pulvermüller et al., 2010). Whilst little work in SD has focussed specifically upon the semantic analysis of auditory objects, limited evidence suggests the involvement of similar processes (e.g., Bozeat et al., 2000).

Evidence for the involvement of multi-modal semantic representations in auditory object recognition is provided by rare reports of auditory associative agnosia, i.e., the selective impairment of semantic processing in the auditory modality only, despite adequate auditory perception (Spreen et al., 1965; Eustache et al., 1990; Peretz, 1996; Garrido et al., 2009; Hailstone et al., 2010). Notably, these reports tend to describe category-specific semantic deficits variously affecting environmental sounds (Spreen et al., 1965), voices (Garrido et al., 2009; Hailstone et al., 2010), and musical melodies (e.g., Eustache et al., 1990; Peretz, 1996). This literature therefore indicates that auditory object recognition may involve both modality- and category-specific mechanisms, and thus multi-modal semantic representations (see section 1.5.5.2). However, for several reasons these conclusions must be treated cautiously. Firstly, many of the available case reports of auditory associative agnosia fail to rule out the presence of additional perceptual impairments which might interact with semantic processes, thus partially accounting for observed deficits (Spreen et al., 1965; Peretz, 1996; Ayotte et al., 2000; Garrido et al., 2009); moreover, interactions between auditory semantic and perceptual processes are supported by at least one further neuropsychological study (Clarke et al., 1996). Secondly, whilst there is some tendency towards left-sided brain damage (Eustache et al., 1990; Lechevalier et al., 1995; Ayotte et al., 2000), the anatomical evidence is conflicting, suggesting the involvement of multiple regions and thus cognitive processes. Taken together, although reports of category-specific auditory associative agnosia tentatively indicate the involvement of multi-modal semantic representations in auditory object recognition, a detailed examination of cases suggests the close association of such processes with other (e.g., perceptual) mechanisms throughout distributed cortical regions.

Functional magnetic resonance imaging (fMRI) studies of healthy brains provide complementary information about mechanisms of auditory object recognition. In the visual and verbal modalities, fMRI findings suggest that neural mechanisms of semantic object analysis partially overlap with those required for object perception (Martin and Chao, 2001; Martin, 2007), thus implicating multi-modal semantic representations in processing. Further, such multi-modal semantic mechanisms, like their perceptual counterparts, are activated in a category-specific manner throughout temporal, inferior parietal, and occipital lobes (Martin and Chao, 2001; Martin, 2007). Although the literature is more limited, similar conclusions emerge from analogous studies in the auditory modality. For example, fMRI studies provide evidence for category-specific multi-modal semantic mechanisms of auditory object processing within temporo-parietal regions (Lewis et al., 2005; Lewis et al., 2006; Lewis et al., 2010; Engel et al., 2009): imitable action sounds (e.g., tool movements) and non-imitable sounds (e.g., animal vocalisations) are processed in dorsally and ventrally directed cortical networks respectively. Additionally, auditory object recognition activates areas that are similar to those implicated in auditory perceptual processing (Engel et al., 2009; Staeren et al., 2009; Leaver and Rauschecker, 2010; Lewis et al., 2010); this partial anatomical overlap may indicate both the relative independence of perceptual and semantic processes, and the presence of important perceptual-semantic interactions (Engels et al., 2009; Staeren et al., 2009; Leaver and Rauschecker, 2010; Lewis et al., 2010). Notably, these fMRI experiments do not tend to implicate the temporal poles and by inference amodal representations in auditory object recognition, and therefore diverge from the predictions of neuropsychological (e.g., Bozeat et al., 2000) and rTMS work (e.g., Pobric et al., 2007); however, this discrepancy is likely due to methodological factors which decrease the likelihood of signal detection in the anterior temporal lobes (Visser et al., 2010). Moreover, a recent fMRI study which minimised signal loss in the ATLs implicates a bilateral ventral portion of this region in the semantic processing of information presented in three different modalities (auditory verbal, auditory non-verbal, visual), indicating amodal processes (Visser and Lambon Ralph, 2011). In contrast, this study associated the left superior ATL with semantic processing in the auditory modality (for both verbal and non-verbal sounds), suggesting the additional presence of multi-modal mechanisms. This study thereby provides evidence for functional

differentiation within the ATLs, and may suggest a graded continuum during auditory object analysis between multi-modal mechanisms in superior areas and amodal representations in more inferior regions. Taken together, fMRI studies of healthy subjects suggest that the recognition of auditory objects depends upon a large distributed temporo-parietal network incorporating closely associated mechanisms of perceptual and category-specific multi-modal semantic processing; additionally, a role for amodal semantic processing in the ventral anterior temporal lobes is also indicated.

Considered side-by-side, there is considerable agreement between the neuropsychological and neuroimaging literatures: both suggest that auditory object recognition relies upon a range of perceptual and semantic sub-processes distributed predominantly throughout the temporal and inferior parietal lobes. However, the auditory neuroscience literature has thus far exhibited a bias towards the examination of healthy brains, and additional studies involving damaged brains are required in order to discriminate essential from ancillary substrates (Price and Friston, 2002). Unlike acquired or simulated brain lesions, the degenerative dementia syndrome of SD delineates a functionally coherent cortical network associated with semantic processing (Seeley et al., 2009); the analysis of this cognitively and anatomically specific disease profile using high resolution functional imaging techniques thereby provides a powerful means to examine brain mechanisms of semantic processing. Thus, the current study sought to use fMRI to investigate auditory object recognition in patients with SD, compared to healthy controls. Experimental conditions were designed to compare perceptual and semantic stages of environmental sound processing (using filtered and raw sounds respectively); and to compare the processing of sounds in two different semantic categories (animals, tools).

5.3 Hypotheses

The hypotheses of this study were threefold. Firstly, it was predicted that auditory perceptual processing would engage similar auditory and peri-Sylvian cortices in SD patients and healthy controls. Secondly, it was predicted that SD would be associated with an alteration in anterior temporal lobe mechanisms

involved in auditory semantic processing. Thirdly, it was predicted that the SD and healthy control groups would differentially activate separable ventral and dorsal anatomical networks for processing animal and tool sound categories respectively.

5.4 Methods

5.4.1 Subjects

Nine consecutive patients (6 males; mean age 64.7 (5.1) years; seven right-handed) who met consensus criteria (Neary et al., 1998) for a diagnosis of SD were recruited from the tertiary cognitive disorders clinic at the National Hospital for Neurology and Neurosurgery, London, UK. Twenty-two healthy control subjects (12 males; mean age 65.1 (6.8) years; 19 right-handed) with no history of neurological or psychiatric illness also participated. Demographic and general neuropsychological data for all subjects are summarised in Table 5.1. Patient and control groups did not differ significantly in age ($p>0.9$), gender ($p>0.5$) or years of education ($p>0.2$). In all patients, the syndromic diagnosis of SD was supported by structural brain MRI showing a typical profile of asymmetric (predominantly left-sided) anterior temporal lobe atrophy. All patients had a general neuropsychological assessment confirming a semantic memory deficit relative to the control group; most patients had associated deficits of verbal intelligence, visual object naming and recognition memory, but performed within the normal range on measures of non-verbal intelligence, working memory and visual object perception, in line with a diagnosis of SD. One patient and two control subjects gave a clinical history of mild peripheral hearing loss. In all subjects, peripheral hearing was assessed at 0.5, 1, 2, 3, 4 kHz using a previously described procedure (section 3.4.2). Separate linear regression models were used at each of the frequencies screened to investigate the effect of group on hearing level (with covariates of age and gender), revealing no significant differences between patients and controls ($p > 0.05$, based upon bootstrapped 95% confidence intervals, bias corrected and accelerated with 2000 replications).

All subjects gave written informed consent to participate and the study was conducted in accord with the guidelines laid down in the Declaration of Helsinki.

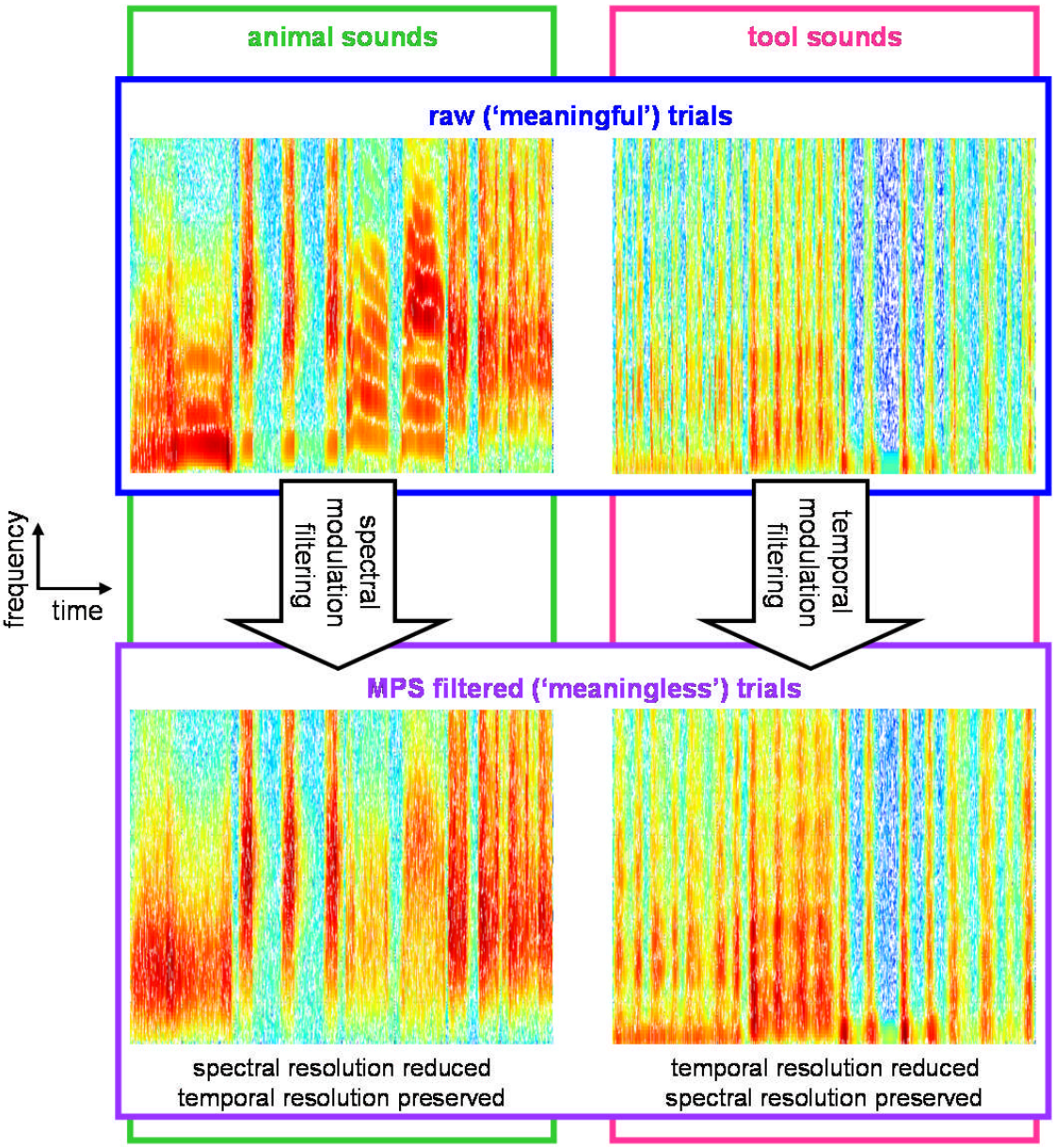
5.4.2 Stimuli

64 animal sounds and 64 tool sounds were selected from on-line databases (e.g., www.sonomic.com) according to the following criteria: (i) all sounds were clear representations of a familiar environmental sound source; (ii) tool sounds were associated with a stereotypical action (e.g., using a handsaw to cut wood; using a broom to sweep the floor); (iii) animal sounds were vocalisations with salient harmonic content (animal movement sounds and noisy animal vocalisations, e.g. roaring, were excluded as potentially perceptually confusable with tool sounds). Sounds chosen were unique exemplars; however, particular sound sources were represented in the set more than once (e.g., the sound set contained four distinct exemplars of a cow lowing). Individual sounds were shortened to 2s samples that retained characteristic acoustic features of the sound source. All sound sources used, with their frequencies of occurrence in the set, are listed in Table 5.3 in the chapter appendix.

To create experimental trials for use during scanning, individual sounds were concatenated into sequences each comprising four different sound sources within the same sound category (tool or animal) with total duration 8s. A set of 32 ‘meaningful’ trials (16 animal, 16 tool) was created using all 128 raw sounds once. Meaningful trials were then manipulated to create a matching set of 32 ‘meaningless’ trials, using a procedure developed by Theunissen and colleagues (Elliott and Theunissen, 2009) which removes identity information whilst preserving spectrotemporal complexity. This procedure operates over the sound’s modulation power spectrum (MPS), i.e., the amplitude spectrum of the 2D Fourier transform of the sound’s time-frequency representation (spectrogram). Rather than describing acoustic content at any particular point in time (as in a spectrogram), the MPS details modulations over time in both the temporal and spectral domains. MPS filtering enables the removal of energy corresponding to particular temporal and/or spectral modulation ranges (i.e., it reduces spectral or temporal ‘resolution’). For complex broad sounds, low-pass spectral filtering will preserve the temporal envelope of the original sounds and low-pass temporal modulation filtering will preserve the overall power spectrum of the sound (see Figure 1). Modulation filtering is a multistep procedure that can be briefly described as follows: (1) obtain a time-frequency representation of the sound (here the log of the spectrogram); (2) take the 2D Fourier

Transform (FT) of this representation to obtain the modulation amplitude and phase spectrum; (3) digitally filter specific temporal-spectral modulations by setting the corresponding amplitudes to zero; (4) invert the modulation spectrum to obtain a desired time-frequency representation of the modulation filtered sound; (5) invert the time-frequency representation to obtain the modulation filtered sound. This last step is achieved using a recursive spectrogram inversion algorithm. In order to remove key cues to sound identity for each sound category, animal and tool sounds were low-pass MPS-filtered in the spectral and temporal domains respectively (since vocalisation identity tends to be more dependent on spectral modulation content and tool identity on temporal modulation content); low-pass cut-off values were 0.5 cycles/kHz for animal sounds and 4Hz for tool sounds. Additionally, to guard against differences between conditions associated with any potential signal-loss effects from the spectrographic inversion in the MPS filtering procedure, the meaningful sounds were subjected to a ‘control’ filtering procedure which consisted of steps (1) and (5) above. Auditory examples of matching meaningful (raw) and meaningless (MPS-filtered) trials are provided (sound examples 70-77).

Figure 5.1 Example spectrograms of tool and animal sounds from 'meaningful' and 'meaningless' sound conditions



To create 'meaningless' trials, 'meaningful' (raw) trials were subjected to low-pass MPS filtering, using a procedure by Elliot and Theunissen (2009); see text for details. Animal trials were filtered in the spectral domain (cut-off point 0.5 cycles/kHz), whilst tool trials were filtered in the temporal domain (cut-off point 4Hz). Low-pass MPS filtering preserves the overall spectrotemporal content of the sounds, but the resolution of spectral and temporal content is lower in the 'meaningless' animal and tool sounds, respectively. This procedure removes cues to sound identity while preserving an acoustically complex percept. Auditory examples are provided (sounds 70-77).

5.4.3 fMRI paradigm

Four experimental sound conditions each comprising 16 trials were presented in a 2x2 factorial design: (i) 'meaningful' trials comprising sequences of raw animal sounds (mful_a); (ii) 'meaningful' trials comprising sequences of raw tool sounds (mful_t); (iii) 'meaningless' trials comprising sequences of MPS-filtered animal sounds (mless_a); (iv) 'meaningless' trials comprising sequences of MPS-filtered tool sounds (mless_t). An additional low-level baseline condition comprised eight silence trials. Trials were presented in two scanning runs, yielding a total of 72*2 = 144 experimental trials. In each run, trials were presented in a random order that was fixed for all subjects. Stimuli were delivered binaurally via electrodynamic headphones (MR Confon GmbH, Magdeburg, www.mr-confon.de) at a comfortable sound pressure level (at least 70 dB). In order to minimise cognitive processing demands in the scanner, subjects listened passively to the stimuli with their eyes lightly closed; no in-scanner output task was used.

5.4.4 Brain image acquisition

All brain images were acquired on a 3Tesla scanner with 12-channel head coil (Magnetom Trio, Siemens). Single-shot gradient-echo (echoplanar image, EPI) volumes were acquired with the following parameters: 48 oblique transverse slices*;* slice thickness 2 mm; inter-slice gap 1 mm; $\alpha = 90^{o}$; echo time (TE) 30 ms; bandwidth 2298 Hz/pixel; bandwidth in phase-encoding (PE) direction 47.3 Hz/pixel; PE direction anterior-posterior; field of view (FOV) 192x192 mm^2; echo spacing 0.5ms; matrix size 64x64; 13% phase oversampling in the PE direction; fat suppression; descending slice acquisition order. The FOV was positioned to ensure coverage of the entire brain. Blood-oxygen-level-dependent (BOLD) signal losses in the temporal lobes due to susceptibility artifacts were minimized by applying a z-shim gradient moment of +0.6 mT/m*ms, a slice tilt of -30^{o}, and a positive PE gradient polarity (Weiskopf et al., 2006). To avoid interaction of the stimulus-induced BOLD responses with the response evoked by the gradient noise of the scanner, a 'sparse-sampling' acquisition paradigm was used with fixed time-to-repeat of 11.4s. EPI acquisitions were triggered externally via a laptop running a customised script under MATLAB 7.0 (The Mathworks^{TM}). Within each run, 74 brain volumes were acquired for each subject (corresponding to 72 trials, plus two initial dummy scans to allow signal

equilibration). To correct for geometric distortions due to B0 field variations, field maps were acquired for each subject after the second run (Cusack et al., 2003; Hutton et al., 2002). For the field map, a double-echo FLASH (GRE) sequence with the following parameters was used: TE1=10ms; TE2=12.46ms; 3x3x2mm resolution; 1mm gap.

Volumetric structural MR brain images were acquired using a T1-weighted 3D MDEFT sequence (Deichmann et al., 2004) with the following parameters: sagittal partition direction; 176 partitions; FoV 256x240 (or 256x256 for subjects with larger heads); matrix 256x256; 1^3mm resolution; TE 2.48ms; repetition time 7.92ms; flip angle 16 degrees; inversion time 910ms; 50% inversion time ratio; fat saturation angle=160 degrees; flow suppression angle=110 degrees; bandwidth=195 Hz/pix; total acquisition time=13 minutes 43 seconds. Two patients with SD did not have structural MRI acquisitions.

5.4.5 Out-of-scanner behavioural assessment

Immediately after scanning all subjects completed a novel environmental sound recognition test using 48 of the raw ('meaningful') sounds delivered in the scanner (24 animals, 24 tools). Individual sounds (each 2s in duration) were played in a fixed random order; subjects were asked to match each sound with its picture from an array of six colour photographs.

5.5 Analysis of fMRI data

Image pre-processing and statistical analyses were performed using Statistical Parametric Mapping software (SPM8©; www.fil.ion.ucl.ac.uk/spm). Field maps were reconstructed to obtain voxel displacement maps (VDMs). Images in each scanning run were separately realigned and unwarped using the corresponding VDM to correct for geometric distortions (one SD and one healthy subject did not have a field map; in these subjects, realignment and unwarping were performed without VDM correction, and this methodological difference was accounted for in subsequent statistical modelling). EPIs were then co-registered to the subject's structural MR image, where available.

The resulting native space EPI images were entered into a first-level (within-subject) general linear model (Friston et al., 1994). The evoked haemodynamic response for each stimulus was modelled as a boxcar convolved with a generic haemodynamic response function and sampled at the end of each trial. The design matrix contained both runs, with run-specific regressors for each of the five conditions and six movement-correction parameters obtained from the realign and unwarp steps. Experimental contrasts were constructed as follows: all sound conditions over silence baseline [(mful_a + mful_t + mless_a + mless_t) - 4*silence], to identify brain areas associated with sound processing; meaningless sound conditions over silence baseline [(mless_a + mless_t) – 2*silence], to identify areas associated with perceptual processing of spectrotemporally complex sounds; meaningful sound conditions over meaningless sound conditions [(mful_a + mful_t) – (mless_a + mless_t)], to identify areas associated with semantic processing of sounds; the meaningful animal sound condition over the meaningless animal sound condition [m'ful_a – m'less_a], to identify areas associated with semantic processing of animal sounds; the meaningful tool sound condition over the meaningless tool sound condition [m'ful_t – m'less_t], to identify areas associated with semantic processing of tool sounds; the semantic processing of animal sounds over the semantic processing of tool sounds [(mful_a – mless_a) – (mful_t – mless_t)] and the reverse contrast [(mful_t – mless_t) – (mful_a – mless_a)], to identify areas associated with category-specific semantic processing favouring animal and tool sounds, respectively. For each subject, each contrast image was normalised to MNI space via unified segmentation (Ashburner and Friston, 2005) of the subject's mean functional brain image. Normalised images were smoothed with an isotropic Gaussian kernel of 8 mm full-width at half-maximum.

Individual contrast images were entered into a second-level (between-subject random effects) model to assess differences between SD and control groups: i.e., the interaction between group and experimental condition. Inter-subject variation in the use of VDMs during realignment and unwarping was modelled as a nuisance covariate, and variances for SD and control groups were allowed to differ. T-contrasts were thresholded at $p<0.001$ uncorrected to form clusters, whose extents were then assessed for family-wise error (FWE) corrected significance at $p<0.05$ over the whole brain. Statistical parametric maps were

displayed on a composite structural brain image constructed as the mean of all individual patient and control normalised structural brain images (each individual structural image was normalised to MNI space using subject-specific parameters derived from unified segmentation of the corresponding mean functional brain image).

Comparing groups within experimental conditions raises a problem of interpretation, in that any differences could in principle be attributable to increased activity for one group in the 'forwards' contrast (e.g., [meaningless sounds > silence]), or increased activity for the other group in the corresponding reverse contrast (e.g., [silence > meaningless sounds]). This issue is particularly relevant to the functional imaging of patients with neurodegenerative brain disease, who might in principle show either increased or decreased levels of cortical activity. Accordingly, a masking procedure was employed to discriminate between these alternate possibilities. Specifically, all forwards contrasts showing increased activity for one group (e.g., patients > controls in [meaningless sounds > silence]), were masked with the reverse contrast in the other group only (e.g., controls in [silence > meaningless sounds]); masking was performed both inclusively and exclusively, using a lenient masking threshold ($p<0.05$ uncorrected). Regions retained after inclusive masking are more likely to index the reverse contrast (e.g., controls>patients in [silence > meaningless sounds]), whilst regions retained after exclusive masking can be attributed to the forwards contrast (e.g., patients > controls in [meaningless sounds > silence]). fMRI in neurodegenerative disease raises a further interpretational issue due to the presence of regionally atrophic cortex: functional changes could reflect alterations within the zone of damage or associated changes in areas of structurally normal (or less affected) cortex. In order to compare the distribution of altered sound processing with the distribution of structural brain damage in the SD group, an atrophy map for the SD group was constructed by comparing structural brain images in the SD and healthy control groups using voxel-based morphometry (VBM); further details are provided in the chapter appendix (Figure 5.4 and legend).

Data from the category-specific semantic contrast were compared with previously reported patterns of category-specific cortical activity. Local maxima

showing preferential bilateral activation for either animal or tool sounds were derived from a previous study by Lewis and colleagues (2005), comprising two 'animal sound' foci (in left and right middle superior temporal gyrus, mSTG), and four 'tool sound' foci (in left and right posterior lateral sulcus, pLaS, and left and right posterior middle temporal gyrus, pMTG). Coordinates were transformed from Talairach into MNI stereotactic space using a validated conversion algorithm (tal2icbm_spm, www.brainmap.org/icbm2tal/; Lancaster et al., 2007). For each subject, effect sizes in the category-specific semantic contrast for the present study were sampled at each of the six foci. The significance of effects within and between groups was assessed using the same model as the main fMRI analysis.

Further separate sub-analyses were conducted in the SD group only, incorporating out-of-scanner behavioural data (see Table 5.1). These sub-analyses were designed to determine whether general semantic performance and explicit sound recognition performance were associated with activation in two key contrasts: perceptual processing ([meaningless sounds > silence]) and category-specific semantic processing. Patient scores on a word-picture matching task (The British Picture Vocabulary Scale, Dunn et al., 1982) were used to index general semantic performance, whilst scores on the novel sound-picture matching task were used to index explicit sound recognition performance. In separate sub-analyses, data from each key contrast was entered into a second-level linear regression model including one of the two behavioural measures. In each sub-analysis, both positive and negative correlations between activation and the behavioural measure were evaluated. Results were assessed using cluster-extent statistics at a family-wise error (FWE) corrected threshold of $p<0.05$ over the whole brain, as before.

5.6 Results

5.6.1 Out-of-scanner behavioural assessment

Most patients performed below the control range on the out-of-scanner sound-picture matching task (see Table 5.1). The control group performed significantly better for recognition of animal sounds than tool sounds (t-test: mean difference=1.8; 95% confidence interval=0.8 to 2.9), but the absolute discrepancy in scores between categories was small (Table 5.1). The SD group

was equivalently impaired for recognition of animal and tool sounds (t-test: mean difference=0.3; 95% confidence interval = -1.9 to 2.6); an analysis of patient scores using the binomial distribution showed that 6/9 patients performed significantly above chance. Taken together these results suggest that any discrepancies in recognition difficulty between sound categories were minor, and that patients were equivalently impaired in the explicit identification of both sound categories.

5.6.2 fMRI data

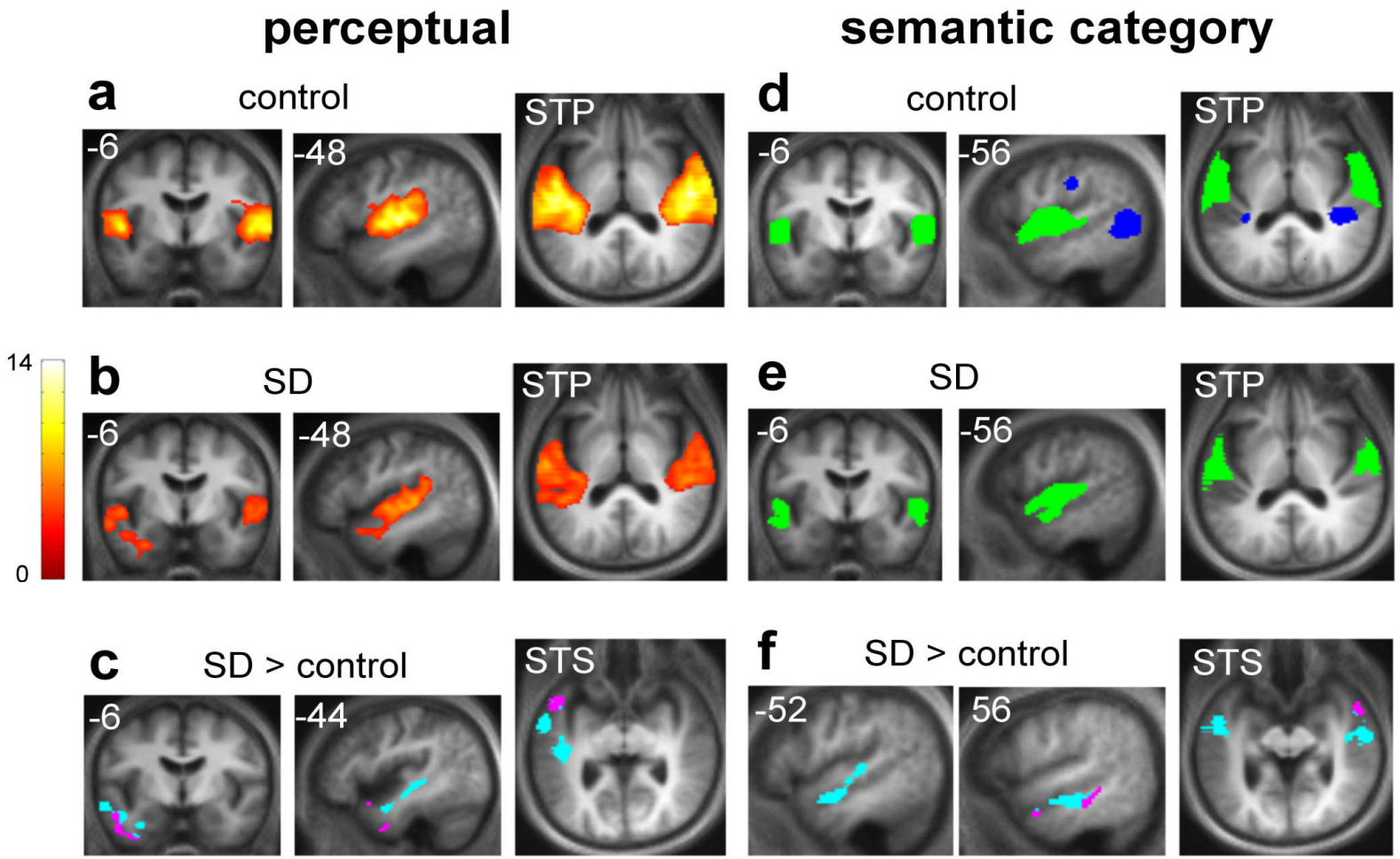
In describing the fMRI findings we focus on two key contrasts showing areas associated with perceptual processing [meaningless sounds > silence] and areas associated with category-specific semantic processing; and comparisons between the SD and healthy control groups. Significant clusters for the key experimental contrasts (all $p<0.05$ after whole-brain FWE correction) are presented in Table 5.2; corresponding statistical parametric maps are shown in Figure 5.2. Further contrasts are described Table 5.4, in the chapter appendix. Additionally, the spatial extent of fMRI signal coverage achieved in this study, via the use of scanning parameters designed to minimise signal loss in the anterior temporal lobes, is indicated in Figure 5.5, also in the chapter appendix.

Table 5.1 Subject characteristics and general neuropsychological performance

	Individual patients									Control group
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**	**Case 9**	**mean (std. dev.); min.**
Sex	m	m	m	m	f	m	f	f	m	10 m, 12 f
Handedness	r	r	r	r	l	r	r	r	l	19 r, 3 l
Age (yrs)	76	64	63	70	63	63	58	65	60	65.1 (6.8)
Education (yrs)	18	10	16	20	10	10	10	12	13	15.1 (3.8)
Disease duration (yrs)	3.3	4.3	5.2	4.9	8.4	5.2	6	7	8	-
MMSE (/30)	29	27	26	24	22	15	12	2	1	29.3 (0.9); 27
Verbal IQ	78	**55**	**57**	83	**55**	**55**	**55**	**55**	**55**	-
Performance IQ	119	92	120	133	100	**71**	91	99	114	-
RMT - words (z score)	0.7	**-1.7**	**-1.7**	-1.3	**-1.7**	**-1.7**	**-1.7**	**-1.7**	**-1.7**	-
RMT - faces (z score)	**-1.7**	**-1.7**	-0.7	**-1.7**	**-1.7**	**-1.7**	**-1.7**	**-1.7**	**-1.7**	-
DS - forwards (z score)	1.5	0.0	-0.5	**-1.7**	-1.0	0.6	**-1.7**	-3.0	**-1.7**	-
DS - backwards (z score)	1.0	1.0	1.5	0.3	-0.3	0.8	**-3.0**	-0.8	-3.0	-
Visual object naming (z score)	**-1.7**	**-1.7**	**-1.7**	**-1.7**	**-1.7**	**-1.7**	**-1.7**	**-1.7**	**-1.7**	-
Arithmetic (z score)	1.6	0.4	1.6	-0.6	**-2.2**	-1.0	**-2.3**	**-2.3**	**-2.3**	-
Visual object perception (z score)	-0.3	0.7	0.7	0.3	-1.3	-0.7	-0.7	0.3	-1.3	-
Word-picture matching (/ 150)	85	102	88	145	40	77	5	5	5	148.2 (1.1); 146
Snd.-pic. matching - animal (/ 24)	9	12	14	23	12	10	4*	7*	0*	21.7 (1.9); 15
Snd.-pic. matching - tool (/ 24)	10	17	14	20	8	10	6*	3*	0*	19.9 (2.1); 16
Synonyms - concrete (z score)	-	**-5.2**	**-7.9**	**-4.1**	**-6.3**	**-6.8**	**-6.8**	-	-	-
Synonyms - abstract (z score)	-	**-3.3**	**-4.7**	-0.9	**-4.7**	**-4.0**	**-3.3**	-	-	-

Scores were transformed into standardised (IQ or Z) scores based on normative data where available. KEY: bold, patient performance lower than 5th percentile (IQ < 75, Z < -1.67); underlined, patient performance lower than minimum control score; *, patient performance not significantly different to score expected by chance, calculated using the binomial distribution; -, not tested; Arithmetic, Graded Difficulty Arithmetic test (Jackson and Warrington, 1986); DS, Digit Span test from Wechsler Memory Scale – Revised (WMS-R, Wechsler, 1987); Intelligence, verbal/ performance intelligence quotient (Wechsler Abbreviated Scale of Intelligence, Wechsler, 1999); max., maximum; min., minimum; MMSE, Mini-Mental State Examination (Folstein et al., 1975); RMT, Recognition Memory Test (Warrington, 1984); Snd.-pic. matching, novel sound-picture matching test based upon stimuli from the main fMRI experiment (see text); Synonyms, single word comprehension (Warrington, McKenna and Orpwood, 1998; normative data taken from a local unpublished study by S Connell, EK Warrington, and SJ Crutch); Visual object naming, Graded Naming Test (McKenna and Warrington, 1983); Visual object perception, Object Decision Test from Visual Object and Space Perception Battery (VOSP, Warrington and James, 1991); Word-picture matching, British Picture Vocabulary Scale (Dunn et al., 1982).

Figure 5.2 Statistical parametric maps showing activation profiles for perceptual and semantic processing of environmental sounds in healthy controls and patients with semantic dementia



Statistical parametric maps (SPMs) are thresholded at p(cluster)<0.05, using family-wise error correction for multiple comparisons across the whole brain. SPMs are rendered on a composite mean normalised structural brain image (see text); the left hemisphere is shown on the left for all coronal and axial sections. For sagittal and coronal sections the plane is indicated using MNI coordinates. All axial slices are tilted parallel to the superior temporal plane to show key auditory regions; the anatomical plane of view is indicated. KEY: SD, semantic dementia; STP, superior temporal plane; STS, superior temporal sulcus. The colour key follows. Panels **a** and **b:** the colour bar (left) codes voxel-wise T scores for contrast [meaningless sound > silence]. Panel **c:** magenta codes clusters showing a significant interaction with group for the contrast [meaningless sound > silence] after inclusive masking with the reverse contrast [silence > meaningless sound] in the control group; cyan codes clusters showing a significant interaction with group for contrast [meaningless sound > silence] after exclusive masking with the reverse contrast [silence > meaningless sound] in the control group. Panels **d** and **e**: green codes significant clusters in the contrast assessing category-specific semantic processing favouring animal sounds, blue codes significant clusters in the contrast assessing category-specific semantic processing favouring tool sounds. Panel **f**, magenta codes clusters showing a significant interaction with group in the contrast assessing category-specific semantic processing favouring animal sounds after inclusive masking with the reverse contrast (category-specific semantic processing favouring tool sounds) in the control group; cyan codes clusters showing a significant interaction with group in the contrast assessing category-specific semantic processing favouring animal sounds after exclusive masking with the reverse contrast (category-specific semantic processing favouring tool sounds) in the control group (see text for further details).

Table 5.2 Summary of significant activation clusters in key experimental contrasts

CONTRAST	meaningless sound > silence				meaningful animal > meaningful tool sound				meaningful tool > meaningless animal sound			
ANATOMY	**k**	**Regions**	**Peaks (x y z)**	**Hem**	**k**	**Regions**	**Peaks (x y z)**	**Hem**	**k**	**Regions**	**Peaks (x y z)**	**Hem**
HC	5298	med HG	-39 -24 8	L	1513	lat HG	-55 -14 8	L	517	pMTG	-57 -58 0	L
		lat HG	-55 -12 10			aSTG	-57 2 -6			TOJ	-57 -70 0	
						pSTG	-63 -26 4		265	insula	-33 -32 18	
										IPL	-59 -24 30	
									218	precuneus	-5 -68 42	
	5094	med HG	53 -16 4	R	1746	lat HG	59 0 4	R	408	pMTG/STS	63 -56 12	R
		PT	55 -24 12			PT	63 -14 6			TOJ	57 -66 6	
						pSTG	69 -20 6		342	insula	35 -28 18	
										PT	41 -36 18	
SD	3608	med HG	-45 -24 -4	L	1713	aSTS/STG	-61 -14 -4	L	-	-	- - -	-
		pSTG	-61 -22 0			PT	-53 -24 2					
						pSTS/STG	-63 -26 4					
	2311	PT	51 -26 10	R	1312	aSTG	59 0 -8	R	-	-	- - -	-
		pSTS/STG	51 -14 -4			pSTS/STG	63 -18 -10					
SD > HC	621	aSTS/MTG	-55 0 -24	L	460	aSTS/MTG	-53 -6 -16	L	-	-	- - -	-
	199	ITG	-51 -14 -34			pSTS/STG	-51 -26 0					
		pSTG/STS	-61 -20 0		448	aSTS/MTG	53 2 -22	R	-	-	- - -	-
						pSTS/ MTG	47 -24 -14					

All cluster-level activations were significant at threshold $p < 0.05$ after family-wise error (FWE) correction for multiple comparisons over the whole brain. For each cluster, extent (k; voxels) and coordinates of local peaks in MNI stereotactic space (mm) are shown. KEY: a, anterior; HC, healthy control group; Hem, hemisphere; HG, Heschl's gyrus; ITG, inferior temporal gyrus; lat, lateral; med, medial; MTG, middle temporal gyrus; p, posterior; PFC, prefrontal cortex; PT, planum temporale; SD, semantic dementia group; STG, superior temporal gyrus; STS, superior temporal sulcus; TOJ, temporo-occipital junction.

In the contrast assessing brain areas involved in perceptual processing of sounds ([meaningless sounds > silence]), both the control group and the SD group showed bilateral activation of superior temporal and peri-Sylvian cortices, including medial and lateral Heschl's gyrus (HG), planum temporale (PT), superior temporal gyrus (STG) and sulcus (STS), and posterior insula (Figure 5.2 a,b; Table 5.2). There was a significant interaction with subject group in left STS, STG, temporal pole, middle temporal gyrus (MTG) and inferior temporal gyrus (ITG). A masking analysis (Figure 5.2 c) suggested that group differences in STS and STG were likely to be attributable to a larger effect for patients than controls in the contrast [meaningless sounds > silence], whereas group differences at the temporal pole and in inferior temporal cortex were likely to be attributable to a larger effect for controls in the reverse contrast [silence > meaningless sounds].

In the contrast assessing category-specific semantic processing favouring animal sounds, both the control group and the SD group showed significant bilateral activation in lateral HG and lateral PT and along STG and STS to the temporal poles (Figure 5.2 d,e; Table 5.2). In the contrast assessing category-specific semantic processing favouring tool sounds, the control group showed significant bilateral activation in a dorsal cortical network including medial PT, posterior insula and MTG (extending to the temporo-occipital junction), precuneus and left inferior parietal cortex; for this contrast no significant activations were identified in the SD group. There was a significant interaction between semantic category and group bilaterally in STG, STS and MTG. A masking analysis (see Figure 5.2 f) suggested that group differences in mid STG and STS were likely to be attributable to a larger effect for patients than controls in the contrast assessing category-specific semantic processing favouring animal sounds, while group differences more anteriorly in STS and inferiorly in MTG were likely attributable to a larger effect for controls than patients in the reverse contrast assessing category-specific semantic processing favouring tool sounds. There was no evidence for significant activation associated with the reverse interaction (i.e., there was no evidence of a larger effect for patients in the contrast favouring tool sound processing nor a larger effect for controls in the reverse contrast favouring animal sound processing). Comparing the activation profiles in the SD group with the

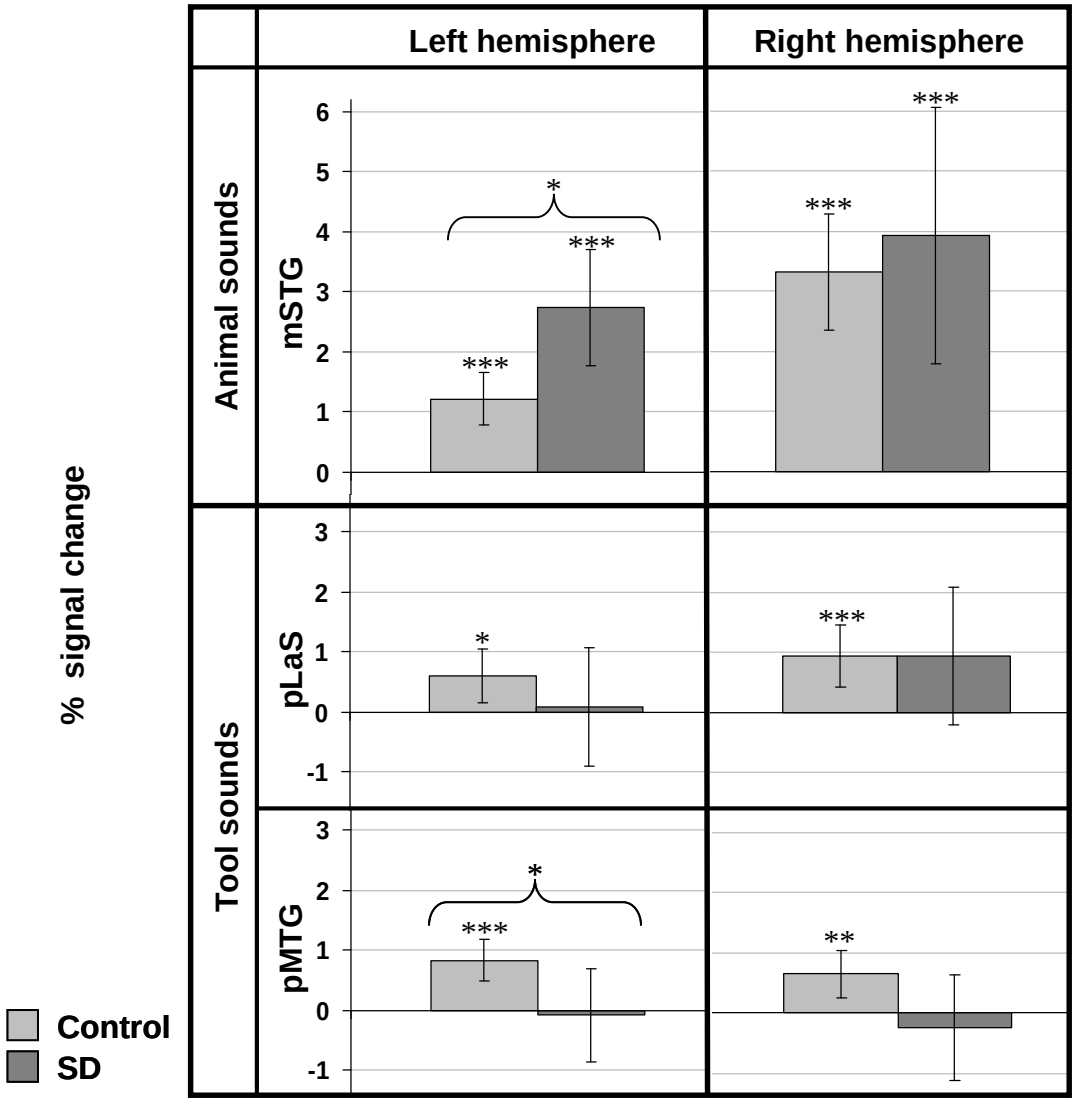
distribution of structural atrophy (see Figure 5.4, chapter appendix), disease-associated functional changes involved areas of atrophic cortex but extended beyond the zone of maximal structural damage: this was particularly evident for alterations of category-specific semantic processing in the right hemisphere for the SD group compared with the healthy control group.

Similar activation profiles were observed in the additional contrasts (Table 5.4, chapter appendix). Activation profiles in the contrast assessing all brain areas involved in sound processing [sound > silence] were similar to the perceptual contrast: both the control group and the SD group showed extensive bilateral activation of superior, anterior and lateral temporal and peri-Sylvian cortices, including medial and lateral HG, PT, STG, STS and posterior insula, with a significant interaction with subject group in bilateral STS, STG, temporal pole, MTG and ITG. In the contrast assessing brain areas involved in semantic processing of sounds combining sound categories [meaningful sounds > meaningless sounds], both the control group and the SD group showed extensive bilateral activation throughout superior temporal and peri-Sylvian cortices including lateral HG, PT, STG, and STS; there was a significant interaction with group in midline cerebellum, however no significant group differences were found in any cerebral regions. Contrasts probing the semantic processing of animal sounds and tool sounds separately ([meaningful animal sounds > meaningless animal sounds]; [meaningful tool sounds > meaningless tool sounds]) were similar to the category-specific versions of these contrasts comparing the two semantic categories directly. In the contrast assessing semantic processing of animal sounds alone ([meaningful animal sounds > meaningless animal sounds]), both groups showed extensive bilateral activation extending anteriorly from lateral HG and PT along STG and STS; and for this contrast there was a significant interaction with group in STS, STG and MTG. In the contrast assessing semantic processing of tool sounds alone ([meaningful tool sounds > meaningless tool sounds]), the control group showed significant activation in bilateral posterior superior temporal, insular and right prefrontal cortex; for this contrast, no significant cortical activations were identified in the SD group and there were no significant differences in cortical activation between the groups.

Further analyses suggested a close correspondence between current data and previously reported patterns of category-specific cortical activity during auditory object processing (Figure 5.3). For the contrast assessing category-specific semantic processing favouring animal sounds, activation in both control and SD groups was significant within the pre-specified animal foci (bilateral middle STG); additionally, the SD group showed greater activity than the control group in the left hemisphere. For the reverse contrast assessing category-specific semantic processing favouring tool sounds, activation in the control group was significant within all pre-specified tool foci (bilateral posterior lateral sulcus, bilateral posterior MTG); however, the SD group did not exhibit significant activity in any of these foci, and there were significant group differences in the left posterior MTG.

In the sub-analyses to examine relations between sound processing and out-of-scanner behavioural performance in the SD group, no significant correlations were found between the perceptual contrast [meaningless sounds > silence] and either behavioural measure. There were significant negative correlations with each behavioural measure in the contrast assessing category-specific semantic processing favouring animal sounds, indicating increased activation associated with decreasing behavioural performance (see Table 5.5 in the chapter appendix). These correlations were restricted to posterior areas beyond the activations associated with the category-specific contrast in the main analysis. No negative correlations were found with either behavioural measure in the contrast assessing category-specific semantic processing favouring tool sounds.

Figure 5.3 Category-specific contrast effects sampled at previously specified foci of category-specific semantic sound processing



Bars show mean effect sizes (proportionate to percent BOLD signal change) for the control and patient groups separately for the category-specific semantic contrast at pre-specified foci of category-specific auditory processing based on Lewis et al. (2005); 95% confidence intervals are also displayed. The left-hand panels show effects at foci previously associated with animal sound processing in the contrast assessing category-specific semantic processing favouring animals, while the right-hand panels show effects at foci previously associated with tool sound processing in the reverse contrast assessing category-specific semantic processing favouring tools. Asterisks above bars indicate significance levels for the control and SD groups separately; asterisks above brackets indicate significance levels for between group comparisons. KEY: *p<0.05; **p<0.01; ***p<0.001; mSTG, middle superior temporal gyrus; pLaS, posterior lateral sulcus; pMTG, posterior middle temporal gyrus; SD, semantic dementia.

5.7 Discussion

Here we have demonstrated altered brain mechanisms of non-verbal sound analysis in patients with SD. A common bilateral cortical network of superior temporal lobe areas was activated during both perceptual and semantic sound processing in the SD group and the healthy control group. Furthermore, the activation profile in control subjects supported previous work showing distinct antero-ventral temporal and posterior temporo-parietal networks for category-specific processing of animal and tool sounds respectively (Lewis et al., 2005; Lewis et al., 2006; Engel et al., 2009; Lewis et al., 2010). However, in comparison to the healthy control group, SD patients showed differential activation of left sided cortical areas in and adjacent to STS both for the perceptual processing of spectrotemporally complex but meaningless sounds, and for the semantic processing of meaningful sounds. Additionally, during perceptual processing patients showed differential activation of left anterior and inferior temporal cortices, and during semantic processing patients showed differential activation of bilateral cortices in the MTG. Further, the abnormal responses of the SD group observed during semantic processing were also indicative of altered brain mechanisms of category-specific auditory object analysis (and particularly, a failure to activate the dorsal cortical pathway for processing tool sounds). Whilst the functional imaging of the anterior temporal lobe is often confounded by artifacts (Visser et al., 2010), current results are unlikely to reflect such problems since parameters were optimised to minimise signal loss in these regions. Additionally, the activation differences in SD were not attributable simply to cortical loss: the activation profile extended beyond the zone of maximal disease-related atrophy, and the SD group showed a preponderant increase in activation compared with the healthy control group. Moreover, activation changes during category-specific semantic sound processing involved cortical areas distinct from the anatomical correlates of out-of-scanner behavioural measures (indexing general semantic and explicit sound recognition impairment). Taken together, these data suggest that SD leads to the abnormal function of brain mechanisms specifically involved in auditory object analysis.

From an auditory neuroscience perspective, the present findings support previous observations both in patients (Clarke et al., 1996; Chapter 2) and in healthy individuals (Engels et al., 2009; Staeren et al., 2009; Lewis et al., 2010; Leaver and Rauschecker, 2010) that indicate a close coupling of perceptual and semantic mechanisms during sound processing. Here, this coupling is suggested by the extensive anatomical overlap between perceptual and semantic processing substrates in the superior temporal lobe in both the healthy control and SD groups (compare Figure 5.2 a,b and Figure 5.2 d,e), and the common involvement of mid and anterior temporal cortices in disease-related alterations affecting both perceptual and semantic levels of analysis (compare Figure 5.2 c,f). It is unlikely that this overlap simply reflects cross-contamination of the semantic category contrast by perceptual stimulus factors, since the contrast here incorporated separate category-specific perceptual baselines closely matched in spectrotemporal complexity to the natural sounds. Further, although this study cannot delineate the specific cognitive sub-processes underpinning cortical activation, the involvement of anterior temporal regions may indicate the disruption of amodal semantic processes (Pobric et al., 2007; Pobric et al., 2010b; Visser et al., 2010b), whilst the involvement of posterior temporal and inferior parietal regions may signify perceptual or multi-modal semantic impairments (Martin and Chao, 2001; Lewis et al., 2005; Lewis et al., 2006; Martin, 2007; Engel et al., 2009; Lewis et al., 2010). Taken together, it may be proposed that results delineate a common brain network at the interface of perceptual and semantic mechanisms (Leaver and Rauschecker, 2010); however, the current data do not resolve the relative contributions made by perceptual and semantic processes, since these were not constrained by a behavioural task during scanning. Nevertheless, the close correspondence between perceptual and semantic deficits observed here in SD, a primary semantic processing disorder, may suggest that auditory semantic mechanisms have a ‘top-down’ modulating effect upon perceptual processes. Additionally, the implication of a contiguous anterior-posterior portion of the STS in disease-related activation patterns might tentatively suggest a graded (rather than binary) interface between perceptual and semantic processes. Notably, each of these conclusions gains strength from previous evidence that SD involves damage to a functionally coherent cortical network (Seeley et al., 2009); however, further work combining both spatial (e.g., fMRI) and temporal (e.g.,

MEG) imaging methodologies is required to resolve these issues. Taken together, the current results suggest that auditory object recognition depends upon a distributed network incorporating closely associated mechanisms of perceptual, multi-modal semantic and amodal semantic processing.

Whilst previous studies of healthy subjects have described the brain mechanisms underpinning category-specific (e.g., animal vs. tool) auditory object recognition (Lewis et al., 2005; Lewis et al., 2006; Engel et al., 2009), the present neuropsychological data provides crucial insights into the causal anatomical substrates and cognitive processes involved. Here, during category-specific semantic sound analysis the SD group showed disease-related activity centred on STS but extending throughout temporal and parietal regions, and additionally failed to activate the dorsal cortical pathway for processing tool sounds. Thus, current findings provide important neuropsychological evidence for the cognitive independence of ventral and dorsal category-specific auditory object processing pathways. Moreover, results implicate distributed temporo-parietal brain regions, previously associated with both auditory perceptual and semantic mechanisms, in category-specific auditory object recognition; further, in the context of degeneration within a functionally coherent cortical network (Seeley et al., 2009), such results are likely to signal the disruption of network-level brain mechanisms. Whilst the failure of patients to activate the dorsal cortical pathway for processing tool sounds might suggest a tool-specific impairment of multi-modal semantic processing, this interpretation is not supported by the explicit sound recognition performance of patients, nor by previous behavioural studies which tend to emphasise equivalent deficits for all types of stimuli (Bozeat et al., 2000; Coccia et al., 2004; Luzzi et al., 2007), and discrepancies between fine-grained categories only (Pulvermüller et al., 2010). Instead, it can be tentatively suggested that disease-related activity during category-specific auditory object recognition may indicate a disruption of links between auditory perceptual and semantic representations; such links may normally support mechanisms for differentiating sound categories prior to subsequent semantic analysis, and furthermore, may hold particular relevance to the processing of tool sounds. In summary, findings suggest that the recognition of auditory categories depends upon a distributed temporo-parietal network involving both perceptual and semantic mechanisms, and that portions

of this network may show relative functional specialization for the processing of particular categories.

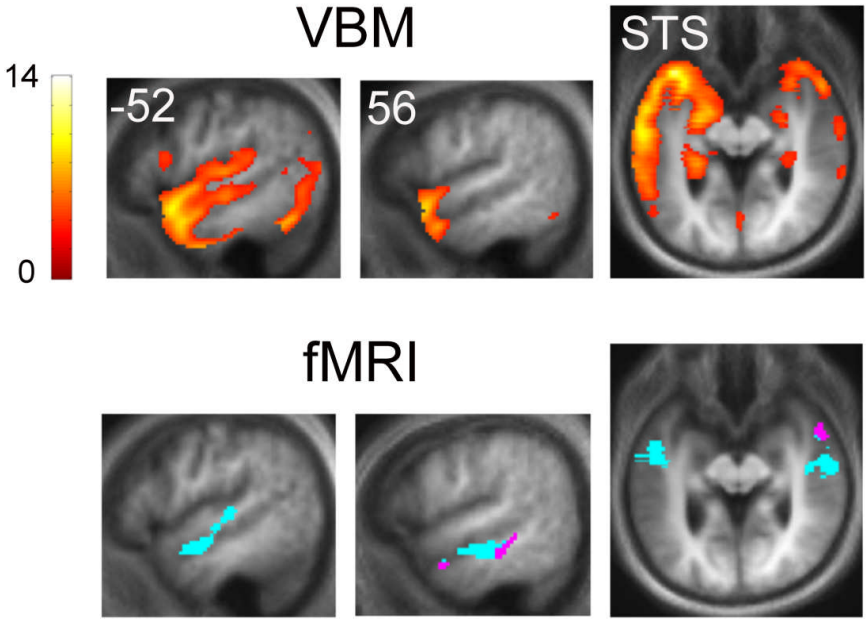
From a disease perspective, the present findings show that SD gives rise to altered profiles of activation compared with the healthy brain; and furthermore, that the direction of disease-related activation changes in SD relative to healthy subjects is not uniform. The most consistent pattern in both the perceptual and semantic processing contrasts here was for increased activation of mid-temporal cortices in SD patients relative to controls; however, there was evidence for a disease-associated decrease in activation relative to controls in more anterior and inferior cortical areas (i.e., differential activation here was driven by greater activation of these areas by controls in the reverse contrasts). This combination of activation changes would fit with structural imaging evidence in SD (Bright et al., 2008; Rohrer et al., 2009): anterior and inferior temporal regions showing the greatest amount of atrophy at all disease stages would account for reduced responses, whilst more posterior and superior areas which become damaged only as the disease evolves could underlie cortical over-activation. It is tempting to conclude that the profile of altered activation in the less affected right hemisphere may both indicate functional abnormalities and foreshadow subsequent atrophy; however, a longitudinal analysis would be required to resolve this issue. In principle, disease-related signal increases within the temporal lobes could reflect the compensatory over-activation of a weakened object processing network; however, such compensation is likely to be inadequate given that there was no evidence for a positive association between cortical activity and sound recognition performance in the SD group. The alterations in object processing mechanisms associated with SD here were neither cognitively nor anatomically restricted: disease-associated changes were observed at both perceptual and semantic levels of object analysis, and the effect of those functional changes (in particular, failure to activate the dorsal cortical pathway for processing tool sounds) extended beyond the temporal lobes. Whereas previous studies of SD have emphasised impairments of amodal processing in association with damage to the anterior temporal lobes (Lambon Ralph et al., 2010), the present findings therefore suggest a more complex derangement of object processing mechanisms involving additional cortical regions, consistent with the emerging picture in the healthy brain (Visser

and Lambon Ralph, 2011). In particular, current evidence may indicate, as already suggested, that deficits in SD are caused by the disease-related modulation of links between perceptual and semantic mechanisms. Whilst this interpretation requires further substantiation, it is consistent with previous evidence that SD is underpinned by damage to neural networks which map onto the large-scale network organisation of the healthy brain (Seeley et al., 2009; Zhou et al., 2010). However, since these studies are based on the analysis of resting state connectivity patterns, the present work adds to the literature by demonstrating network effects in the working brain. In summary, the current results suggest candidate brain mechanisms for a disorder of object recognition in SD, previously proposed on neuropsychological grounds (Warrington, 1975; Bozeat et al., 2000; Coccia et al., 2004; Luzzi et al., 2007; Goll et al., 2010a; Pulvermüller et al., 2010).

This study suggests clear directions for future work. From an auditory neuroscience perspective, the present study did not employ an in-scanner processing task: this imposes an important caveat upon the interpretation of the activation changes, and their behavioural relevance remains to be established. Moreover, the present paradigm did not delineate the specific cognitive representations involved in auditory object recognition (e.g., perceptual, multi-modal semantic, amodal semantic), and it is likely that this issue might be solved only via the convergence of neuropsychological, neuroimaging and computational studies involving comparisons between processing in different modalities during different tasks. Finally, from a disease perspective, there is a need for longitudinal studies to assess how cortical dysfunction in SD relates to irreversible tissue loss; such work holds potential to highlight biomarkers of pathophysiology that could be used to track, monitor and further the understanding of disease progression in this degenerative condition.

5.8 Chapter appendix

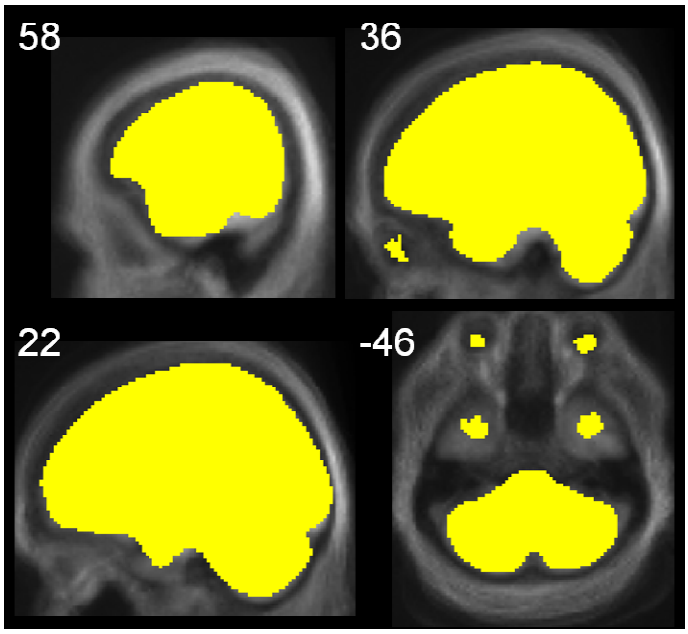
Figure 5.4 Regions of reduced grey matter in the SD group relative to controls



In order to compare activation profiles in the category-specific semantic processing contrast with the distribution of structural brain damage, regions of reduced grey matter volume in the SD group versus controls were assessed using voxel-based morphometry (VBM) in SPM (SPM8; www.fil.ion.ucl.ac.uk/spm). Unified segmentation was applied to all re-orientated structural images (22 controls, 7 patients) to obtain segmentations of grey matter, white matter and cerebrospinal fluid (CSF). Next, using the subject-specific normalisation parameters derived within the main fMRI analysis, grey matter segments were warped to MNI space with modulation. Normalised images were then smoothed with an isotropic Gaussian kernel of 8 mm full-width at half-maximum. Regional differences in grey matter volume between SD and control groups, incorporating age and total intracranial volume (measured as the sum of grey matter, white matter and CSF segmentations outside of SPM; Whitwell et al., 2001) as nuisance covariates, were assessed using voxel-wise T tests, thresholded leniently at $p<0.001$ uncorrected. Statistical parametric maps (SPMs) from the VBM analysis showing significant grey matter change in the SD group relative to controls are displayed in the Figure; also shown are SPMs from the fMRI analysis showing a significant interaction with group for the contrast assessing category-specific semantic processing favouring animal sounds (see Figure 5.2 legend). VBM and fMRI maps are displayed on matching sections from the same group mean normalised structural image; the plane of the sagittal sections is indicated using MNI

coordinates and the axial sections have been tilted to run along the superior temporal sulcus (STS). The VBM analysis shows a typical profile of selective, asymmetric (predominantly left-sided) grey matter atrophy maximally affecting anterior medial and inferior temporal cortices with less severe involvement of more superior and posterior temporal cortices and some extension to frontal lobe areas (voxel-wise T score of grey matter change is coded on the colour bar, left).

Figure 5.5 Spatial extent of fMRI signal coverage



Panels depict three sagittal and one axial section of the binary image used to mask second level results (i.e., group comparisons), overlaid on the composite mean normalised structural brain image (which is also used to display the main results in Figure 5.2). This mask provides an indication of the fMRI signal coverage in the current study, which was enhanced via the use of scanning parameters to minimise signal loss in the anterior temporal lobes (see section 5.4.4). Although the coverage achieved does not encompass the full extent of the temporal lobes, it nevertheless includes the majority of ventral and anterior temporal cortical regions. This mask was created as follows: (i) all subject-specific masks generated during first level statistical analyses were normalised (using subject-specific parameters derived from unified segmentation of the corresponding mean functional brain image) and smoothed (kernel 8mm); (ii) the mean of all smoothed normalised masks was calculated; (iii) finally, this mean image was binarised to create a mask, by applying a threshold calculated using a previously described automatic procedure (opt_thresh.m, Ridgway et al., 2009).

Table 5.3 Sound sources used to construct experimental trials

Animals		Tools	
Sound source	**N**	**Sound source**	**N**
dog	8	slicing food with a knife	6
chimp	5	using a shovel to move dirt/gravel	5
cow	5	filing metal	4
hen	5	hitting with a hammer	4
horse	5	stirring with a spoon/whisk	4
sheep	5	using a broom/rake to sweep the floor	4
domestic cat	4	writing with pencil on paper/chalk on a blackboard	4
duck	4	brushing teeth	3
pig	4	sawing wood	3
sea lion	4	sharpening a knife	3
big cat	3	typing on a computer/typewriter	3
		using a stapler	3
bird	3	using scissors to cut paper	3
		chopping wood	2
donkey	3	loading a gun	2
		peeling a vegetable	2
elephant	3	sanding wood	2
		using a ratchet	2
goose	2	using a sellotape dispenser	2
		locking a door	1
dolphin	1	turning a page of a book	1
		using a hole-punch	1

KEY: N, number of distinct exemplars of each sound source within the sound set.

Table 5.4 Additional significant activation clusters in experimental contrasts

CONTRAST	all sound > silence				meaningful > meaningless sound				meaningful > meaningless animal sound				meaningful > meaningless tool sound			
ANATOMY	k	Regions	Peaks (x y z)	Hem	k	Regions	Peaks (x y z)	Hem	k	Regions	Peaks (x y z)	Hem	k	Regions	Peaks (x y z)	Hem
HC	5326	lat HG	-57 -14 10	L	2572	med HG	-45 -22 2	L	2535	PT	-49 -24 4	L	803	insula	-35 -32 14	L
		med HG	-47 -22 4			insula	-37 -28 12			PP	-49 -6 -4			PT	-43 -34 12	
	946	PFC	-41 14 22			pSTG/STS	-67 -32 12		781	PFC	-43 10 24		219	pMTG	-53 -60 2	
		motor	-51 -6 48		918	PFC	-43 18 26		3195	PT	55 -14 2	R	2112	PT	45 -24 12	R
	223	IC	-1 -40 -6		3688	PT	57 -14 4	R		pSTG	63 -16 0			pSTS/STG	55 -48 6	
		MGN	-15 -26 -4			p STS/STG	63 -34 6			aSTG	57 0 -10		459	PFC	57 28 4	
	5204	med HG	53 -16 4	R	835	PFC	49 32 14		301	PFC	41 14 24					
		PT	61 -14 8													
SD	4370	pSTS/STG	-61 -22 0	L	1941	aSTG	-59 -12 0	L	2807	aSTS/STG	-61 -14 -2	L	-	-	- - -	-
		med HG	-45 -24 -4			pSTS/STG	-61 -40 4			pSTS/STG	-53 -24 0					
	2789	pSTS/STG	53 -12 -6	R	2142	aSTS/STG	57 -8 -10	R	2875	aSTG	57 -2 -10	R	-	-	- - -	-
		PT	51 -26 10			pSTS/STG	49 -16 -2			pSTS/STG	61 -18 -10					
						PT	51 -34 16									
SD > HC	1335	ITG	-47 -2 -40	L	224	Cerebellum	-9 -62 -46	-	453	pSTS/STG	-47 -32 0	L	-	-	- - -	-
		TP	-31 12 -42				-19 -58 -50			aSTS/MTG	-55 2 -22					
	224	ITG	55 -12 -34	R					393	pSTS/STG	59 -18 -12	R	204	Caudate nucleus	21 28 6	R
		aSTS/STG	47 -2 -24				-1 -64 -32			pMTG	51 -28 -18					
										aSTS/MTG	53 4 -26					

All cluster-level activations were significant at threshold $p < 0.05$ after family-wise error (FWE) correction for multiple comparisons over the whole brain. For each cluster, extent (k; voxels) and coordinates of local peaks in MNI stereotactic space (mm) are shown. KEY: a, anterior; HC, healthy control group; Hem, hemisphere; HG, Heschl's gyrus; IC, inferior colliculus; ITG, inferior temporal gyrus; lat, lateral; med, medial; MGN, medial geniculate nucleus; MTG, middle temporal gyrus; p, posterior; PFC, prefrontal cortex; PP, planum polare; PT, planum temporale; SD, semantic dementia group; STG, superior temporal gyrus; STS, superior temporal sulcus.

Table 5.5 Significant associations with out-of-scanner behavioural measures for category-specific semantic sound processing in the SD group

BPVS					
k	**Regions**	**Peaks (x y z)**			**Hem**
84	occipital pole	17	-98	-2	R
76	cerebellum	-25	-68	-20	L
		-29	-74	-24	
Sound recognition					
104	TOJ	-29	-74	-20	L
		-27	-68	-26	
		-17	-66	-18	
83	p cingulate	7	-56	16	L/R
		-3	-60	14	
80	p ITG	33	-62	-16	R
		37	-66	-22	
60	visual cortex	9	-98	0	R
		15	-96	-8	
		19	-96	0	

Clusters indicate regions showing inverse associations with out-of-scanner behavioural measures (BPVS score, sound recognition score) in the contrast assessing category-specific semantic processing favouring animal sounds. All cluster-level activations were significant at threshold $p < 0.05$ after family-wise error (FWE) correction for multiple comparisons over the whole brain. For each cluster, extent (k; voxels) and coordinates of local peaks in MNI stereotactic space (mm) are shown. KEY: BPVS, British Picture Vocabulary Scale (Dunn et al., 1982); Hem, hemisphere; ITG, inferior temporal gyrus; p, posterior; SD, semantic dementia; sound recognition, novel sound recognition test (see text for details); TOJ, temporo-occipital junction.

6 Impairments of auditory scene analysis in Alzheimer's disease

6.1 Summary

Parsing of sound sources in the auditory environment, or 'auditory scene analysis' (ASA), is a computationally demanding operation that is likely to involve multiple auditory-specific ('bottom-up' and 'top-down') and executive sub-processes. This chapter comprises a preliminary neuropsychological characterisation of ASA in two subject groups: 21 patients with typical AD and 20 age-matched healthy controls. A novel auditory dual stream paradigm was designed, based on synthetic sound sequences, to assess auditory-specific processes of ASA; further, two independent measures of these processes were provided through the use of two separate tests ('segregation' and 'grouping'). Additionally, ASA tests were conducted alongside baseline measures of basic auditory perception, task compliance, and neuropsychological functions. Compared with healthy controls, patients with AD had impairments of ASA, and performance in the separate segregation and grouping tests was comparably affected. Further, ASA impairments in AD were not wholly attributable to simple auditory perceptual or task factors. Thus, results suggest that AD leads to the relatively selective impairment of auditory-specific ASA processes, and may indicate the relative independence of corresponding mechanisms in the healthy brain. However, in both tests, between-group differences were partly attributable to non-verbal (visuo-spatial) working memory capacity, and ASA performance was correlated with additional executive neuropsychological measures. The derivation of these results from the study of patients who typically exhibit cortical damage to functionally coherent brain regions (e.g., Seeley et al., 2009) suggests that ASA may be conducted within a distributed network involving close interdependencies between auditory-specific and executive mechanisms.

6.2 Aims of the investigation

The aims of this investigation were twofold: to design a neuropsychological battery suitable for assessing deficits of auditory scene analysis (ASA) in neurological patients; and to use the battery to conduct an initial exploratory investigation of ASA deficits in the typical variant of Alzheimer's disease (AD).

6.3 Background

The literature pertaining to the cognitive psychology of auditory scene analysis was reviewed in detail in the introduction (section 1.5.4); however, a brief summary of findings is presented here to re-familiarise the reader with relevant concepts.

The term auditory scene analysis (ASA; Bregman, 1990) refers to the set of cognitive processes by which the brain makes sense of sound mixtures. Specifically, ASA is required to determine which acoustic properties belong to which sound sources, or in other words, to parse the auditory scene into constituent sound objects (collections of acoustic properties that are bound together and disambiguated from background noise). It is likely that ASA is mediated by several relatively independent processes, including 'bottom-up', 'top-down' and executive mechanisms (Bregman, 1990; Winkler et al., 2009). Bottom-up mechanisms involve the parsing of auditory scenes according to simple acoustic properties such as frequency and amplitude (Bregman, 1990; for a review, see Fishman and Steinschneider, 2010). Top-down mechanisms involve the parsing of scenes according to prior auditory perceptual knowledge stored in the form of 'auditory templates' (Griffiths and Warren, 2002; see also section 1.5.3.6.2); such mechanisms are therefore biased towards the formation of previously encountered objects. Finally, executive mechanisms refer to a heterogeneous range of attentional and working memory processes that support ASA, particularly during the perception of complex multi-object scenes (Naatanen, 1990; Alain and Arnott, 2000; Cusack et al., 2000, 2005).

A growing body of functional imaging work in healthy subjects has implicated a network of brain areas in ASA: these include primary and association auditory

cortices (Deike et al., 2004; Wilson et al., 2007; Gutschalk et al., 2007; Schönwiesner et al., 2007; Deike et al., 2010; Overath et al., 2010; Smith et al., 2010; Schadwinkel and Gutschalk, 2010) and parietal and frontal regions (e.g., Cusack et al., 2005; Schönwiesner et al., 2007). Such studies have begun to define distinct brain substrates and time windows for particular ASA sub-processes. For example, in a combined fMRI-EEG study (Schönwiesner et al., 2007), three distinct cortical regions were associated with temporally successive stages of ASA: primary auditory cortex with initial object segregation (a bottom-up process guided by the perception of auditory properties); posterior superior temporal gyrus and planum temporale with the detailed perceptual representation of segregated objects (a top-down process guided by prior knowledge of auditory objects); and mid-ventro-lateral pre-frontal cortex with attentional allocation (an executive process). Additionally, a number of fMRI studies have emphasised the role of the planum temporale in the top-down process of matching incoming acoustic data with stored auditory templates during ASA (Deike et al., 2004; Wilson et al., 2007; Gutschalk et al., 2007; Overath et al., 2009; Deike et al., 2010; Smith et al., 2010). Further, another fMRI study showed greater activity in the inferior parietal sulcus (IPS) when two streams were perceived compared to one (Cusack et al., 2005), indicating the presence of an executive process for attending to multiple segregated objects within a scene. Taken together, findings suggest that ASA may involve a number of relatively independent bottom-up, top-down and executive mechanisms that occur throughout a network of closely associated brain regions (Schönwiesner et al., 2007; Overath et al., 2009).

Little is known about ASA in human neurological disease. In a group of patients with right parietal damage, Cusack et al. (2000) revealed impairments for attending to multiple segregated objects within a scene, suggesting a critical role for the non-dominant parietal lobe in executive ASA mechanisms. Whilst further neuropsychological data is not yet available, ASA deficits might be predicted in neurodegenerative diseases that involve the posterior temporal and parietal lobes, including progressive non-fluent aphasia (PNFA), logopenic aphasia (LPA), and typical Alzheimer's disease (AD; see section 1.6). In particular, clinical observation suggests that patients with AD may suffer ASA deficits relatively frequently and early on in the course of the disease process.

At presentation, patients with AD commonly complain of difficulty in tracking auditory information streams, for example, when following conversations in the presence of background noise. In both early and pre-symptomatic AD groups, subjects show impairments on verbal tasks that are likely to depend upon ASA processes (Gates et al,. 1996; Gates et al,. 2002; Gates et al., 2008), and altered cortical function during relevant non-verbal auditory tasks (Golob et al., 2007; Golob et al., 2009). Further, given that AD involves the selective degeneration of a functionally-specific temporal lobe episodic memory network (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010), examination of this patient group may provide insight into the proposed network-level mechanisms of ASA (e.g., Schönwiesner et al., 2007; Overath et al., 2009).

This study comprised a systematic neuropsychological investigation of ASA in a cohort of patients with AD. A novel battery was created to probe two generic processes of fundamental relevance to ASA: the segregation of coincident sounds into separate sound objects; and the perceptual grouping of temporally spaced sounds into a single extended object (a sound 'stream'). Given the exploratory nature of this work, these tests were designed to probe bottom-up and top-down ASA mechanisms in combination, rather than separately. However, to dissociate these mechanisms from related processes, tests were designed to minimise extraneous cognitive demands (e.g., for sound identification or labelling), and to explicitly measure the contribution of executive, task-related, and basic auditory perceptual factors that might contribute to overall ASA performance.

6.4 Hypotheses

Hypotheses were twofold: firstly, AD leads to ASA impairments (i.e., bottom-up/top-down) that are at least partially unaccounted for by other cognitive factors, thus providing evidence for relatively independent ASA mechanisms; secondly, ASA impairments in AD are partially influenced by executive processing deficits, suggesting a key role for executive mechanisms in ASA.

6.5 Methods

6.5.1 Participants

Twenty-one consecutive patients (12 females; mean age (years) = 65.0, standard deviation = 7.9) with a clinical diagnosis of typical AD were recruited from a tertiary cognitive disorders clinic. All patients had a structured clinical history and neurological examination by an experienced cognitive neurologist. A diagnosis of AD was based on revised NINCDS-ADRDA criteria for probable AD (Dubois et al., 2007; McKhann et al.,1984) with a corroborating history of episodic or topographical memory impairment as the leading symptom. Patients had brain MRIs showing features typical of AD (bilateral symmetrical hippocampal atrophy with less marked background cerebral atrophy) in all but two cases (one showing diffuse atrophy without hippocampal emphasis, and one with a normal scan); no scan showed significant cerebrovascular damage. Eighteen healthy control subjects (12 females; mean age (years) = 65.7, standard deviation = 7.5) with no history of neurological or psychiatric illness also participated. Patients underwent a comprehensive general neuropsychological assessment in order to provide background data and to assist interpretation of the experimental auditory battery. A subset of these assessments, measuring general (non-auditory) cognitive abilities that might potentially influence performance on the experimental tests, was also completed by controls. These latter assessments comprised digit span (indexing auditory working memory; Wechsler, 1987), visuo-spatial span (indexing non-verbal working memory; Wechsler, 1999), and a reaction time test (indexing a combination of sustained and selective attention, adapted from Stuss et al., 2005; further details provided in the chapter appendix). Subjects with clinically significant hearing loss were excluded from the study; however, given the prevalence of age-related hearing problems in older adult populations, subjects with mild hearing loss were retained, and the ensuing effects upon assessments of auditory cognition were measured (see below). Demographic and general neuropsychological data for all subjects are summarised in Table 6.1. Patient and control groups were well-matched for gender, age and years of education. All subjects gave written informed consent to participate and the study was conducted in accord with the guidelines laid down in the Declaration of Helsinki.

Table 6.1 Demographic and neuropsychological group data

Measure	Units	AD	Control
		Mean (std. dev); unless otherwise indicated	
Gender	m:f	9:12	6:12
Age	years	65.0 (7.9)	65.7 (7.5)
Education		18.5 (3.0)	18.5 (3.8)
Disease duration		5.9 (2.5)	-
MMSE	raw score (/ 30)	22.1 (4.2)	-
WASI VIQ	IQ	101.1 (16.9)	-
WASI PIQ		87.3 (19.4)*	-
BPVS[1]		109.5 (17.4)	
RMT (Words)	Z	-1.4 (0.6)*	-
RMT (Faces)		-1.3 (0.7)*	-
Graded Naming Test		-0.8 (1.5)	-
Arithmetic		-1.1 (1.0)	-
Object Decision		-0.4 (1.2)	-
Stroop (Colour naming)		-1.5 (1.4)*	-
Stroop (Word reading)		-1.2 (1.6)	-
Stroop (Interference)[2]		-1.5 (1.2)*	-
Digit span (forwards)	raw score (/ 12)	**7.5 (2.2)**	9.8 (1.6)
Digit span (reverse)		**5.2 (2.8)**	8.1 (3)
Visuo-spatial span (forwards)		**5.2 (2.5)**	7.4 (2)
Visuo-spatial span (reverse)		**3.9 (2.1)**	7.2 (0.9)
RT, sustained	raw time (ms)	**520.7 (264.9)**	302.8 (79.0)
RT, sustained plus selective		**647.8 (219.4)**	461.8 (88.3)

KEY: *, mean group score <10th percentile of published normative data; bold numbers, AD group differs from experimental control group ($p<0.05$, inferred from bootstrapped confidence intervals); [1] no published normative data exists in older populations and thus normative data for 18 year-old subjects were used; [2] three AD subjects were too impaired to attempt the interference condition of the Stroop test; AD, Alzheimer's disease; Arithmetic, Graded Difficulty Arithmetic test (Jackson and Warrington, 1986); BPVS, British Picture Vocabulary Scale, a test of semantic processing involving word-picture matching (Dunn *et al.,* 1982); Digit span, WMS-R Digit Span (Wechsler, 1987); Graded Naming Test (McKenna and Warrington, 1983); MMSE, Mini-mental state examination (Folstein *et al.,* 1975); Object Decision, test of visual object perception taken from the Visual Object and Space Perception Battery (VOSP, Warrington and James, 1991); RMT, Recognition Memory Test (Warrington, 1984); RT, reaction time test (following Stuss et al., 2005, see chapter appendix); Stroop, D-KEFS Stroop test (Delis, Kaplan and Kramer, 2001); Visuo-spatial span, WMS-III Spatial Span (Wechsler, 1999); WASI VIQ and PIQ, Wechsler Abbreviated Scale of Intelligence (WASI) for measurement of verbal and performance IQ (Wechsler, 1999).

6.5.2 Peripheral hearing assessment

To assess any effects of hearing loss on performance in the experimental tasks, all patients and controls underwent pure tone audiometry using the procedure described in section 3.4.2. All subjects were assessed at the right ear (except one AD patient who reported unilateral right-sided hearing loss and was therefore tested at the left ear).

6.5.3 Assessment of ASA

Two novel neuropsychological assessments were developed to probe generic ASA processes in cognitively impaired subjects: 'ASA-segregation', requiring the segregation of coincident sound objects on the basis of timbral cues; and 'ASA-grouping', requiring the grouping of temporally spaced sound objects into a single stream on the basis of pitch cues. Tests were designed to minimise any requirement for semantic processing of the constituent sounds. However, from a clinical perspective, the segregation task indexes a process involved in recognising a salient sound (e.g., one's own name) within the auditory environment, while the grouping task indexes a process involved in tracking a conversation (e.g., a particular speaker) in the presence of background noise. In order to equate overall stimulus complexity and cognitive demands other than the ASA process of interest, the two ASA assessments were based on similar sound elements and response procedures. Each ASA assessment comprised three sub-tests: the ASA test proper, and two baseline control tests assessing subsidiary cognitive processes which in themselves do not constitute ASA, but which were predicted to affect performance in the ASA tasks. These control tests comprised a 'perceptual-cue' control test, to assess whether subjects could discriminate changes in perceptual cues (pitch or timbre) driving the relevant ASA test; and a 'task-response' test, to assess whether subjects could reliably comply with the task response requirements of the relevant ASA test.

6.5.4 ASA-segregation assessment

6.5.4.1 Main test

Stimuli (N=20) were each created digitally in Matlab (MathWorks^{TM}) by superimposing two sequences of harmonic sounds to create composite continuous sounds with overall duration 10 seconds. A schematic of the test is presented in Figure 6.1, and auditory examples are provided (numbers 82-83).

On every trial, one sound sequence had a timbre designated as the ‘target’ timbre, Tt, while the other had a distinct ‘distractor’ timbre, Td. Four different Td timbres, each distinct from Tt, were randomly distributed across the stimulus set to guard against any idiosyncratic effects that might follow the superposition of a particular timbre pair. Each sound element had the same temporal envelope (amplitude modulated at 80Hz), pitch (283Hz) and bandwidth (2950 Hz); timbre was manipulated by changing spectral shape within this frequency range. On every trial, the Td sequence comprised 1 second intervals of sound separated by 1 second inter-sound gaps. Two experimental conditions were created by varying the temporal pattern of the Tt sequence, which was either continuous (10 trials) or intermittent with 1s intervals of sound separated by 1 second inter-sound gaps mirroring the temporal pattern of the Td sequence (10 trials). In the ‘intermittent’ condition, the intensity level of Td was increased to match the overall intensity level in the ‘continuous’ condition. The task on each trial was to decide whether Tt sounds were ‘always on’ (i.e., continuous) or ‘on and off’ (i.e., intermittent).

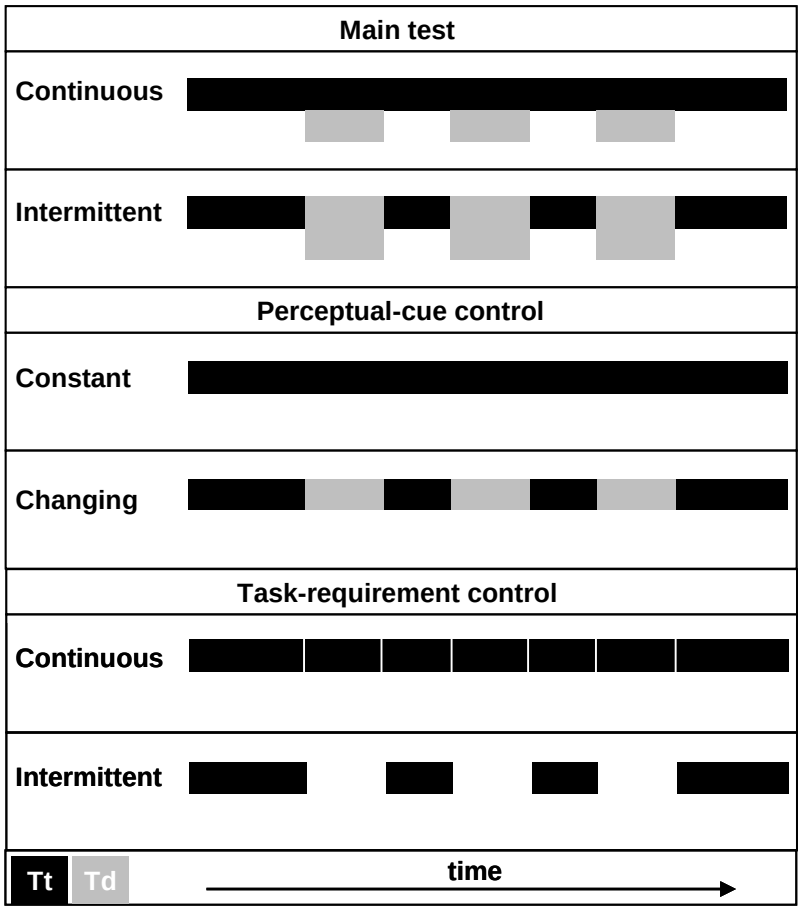
6.5.4.2 Perceptual-cue control

This control test was intended to establish that subjects were reliably able to detect timbre changes. 10 sound sequences were presented, 5 with continuous fixed timbre Tt, and 5 with timbre alternating between Tt and Td (the four distinct Td timbres described above were randomly distributed across the latter 5 stimuli); the temporal pattern of sequences matched those used in the main test (see Figure 6.1, and sound examples 78-79). The task on each trial was to decide if the sound was ‘constant’ or ‘changing’.

6.5.4.3 Task-requirement control

This control test was intended to establish that subjects could comply with task requirements to report continuous and intermittent temporal patterns. 10 sequences of sounds with timbre Tt were presented, 5 continuous and 5 intermittent; the temporal pattern of sequences matched those used in the main test (see Figure 6.1 and sound examples 80-81). The task on each trial was to decide whether the sound was ‘always on’ (i.e., continuous) or ‘on and off’ (i.e., intermittent).

Figure 6.1 ASA-segregation assessment



Conditions in the three subtests of the ASA-segregation assessment (the ASA test and the perceptual-cue and task-requirement control tests) are shown schematically. Oblongs represent individual sound elements; for each element, width indicates relative duration, and depth indicates relative intensity. KEY: Tt, target timbre, Td, distractor timbre. Sound examples are provided (numbers 78-83).

6.5.5 ASA-grouping assessment

6.5.5.1 Main test

Stimuli (N=20) were each created digitally in Matlab (MathWorks^{TM}) by superimposing two sequences of harmonic sounds to create composite sound sequences with overall duration 12 seconds; each individual sound element in a sequence had duration 60 msec with a flat temporal and spectral envelope and fixed frequency bandwidth (2950 Hz). A schematic of the stimuli is presented in Figure 6.2, and auditory examples are provided (numbers 88-89). For every stimulus, one of the component sequences was isochronous (fixed inter-sound interval (ISI) 135msec) and the other sequence was anisochronous (ISI varying pseudo-randomly between 210 and 930ms). Individual sounds were assigned

one of two pitches, either a target pitch (Pt=423Hz) or a distractor pitch (Pd=237Hz); these pitch values were chosen such that they did not align with any familiar tonal interval from western musical scales. To create two experimental conditions, the distribution of Pt and Pd across the sound elements of the two superimposed sequences was varied from trial to trial. In the ‘even’ condition (10 trials), all sounds in the isochronous sequence had pitch Pt, whilst all sounds in the anisochronous sequence had pitch Pd. In the ‘uneven’ condition, Pt was distributed between the isochronous and anisochronous sequences such that the temporal sequence of Pt sounds was itself anisochronous. This design ensured that the overall temporal distribution of sound elements (irrespective of pitch) and the mean rate of presentation of sounds with the target pitch were matched between conditions. The task on each trial was to decide whether Pt sounds were ‘even’ or ‘uneven’.

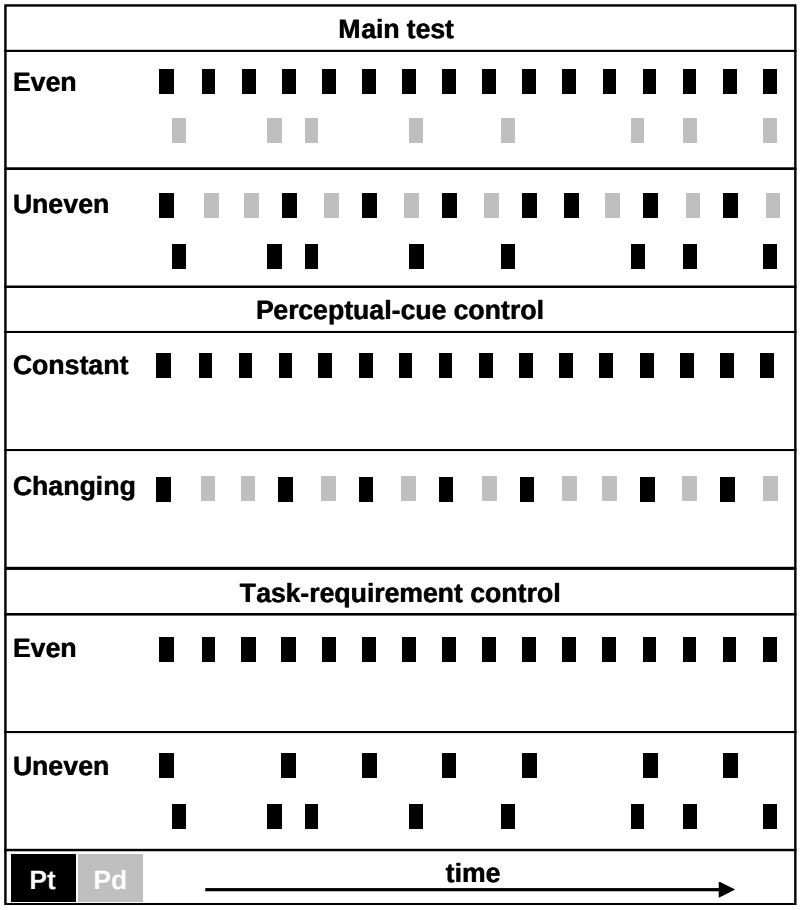
6.5.5.2 Perceptual-cue control

This control test was intended to establish that subjects were reliably able to detect pitch differences. 10 isochronous sequences were presented, 5 with pitch fixed at Pt and 5 with pitch changing between Pt and Pd; the tempi of the sequences matched those used in the main test (see Figure 6.2, and sound examples 84-85). The task on each trial was to decide if the pitch was ‘constant’ or ‘changing’.

6.5.5.3 Task-requirement control

This control test was intended to establish that subjects could comply with task requirements to report even and uneven temporal patterns. 10 sequences of sounds with pitch Pt were presented, 5 isochronous and 5 anisochronous; the temporal pattern of sequences matched those used in the main test (see Figure 6.2, and sound examples 86-87). The task on each trial was to decide whether the sequence was ‘even’ or ‘uneven’.

Figure 6.2 ASA-grouping assessment



Conditions in the three subtests of the ASA-grouping assessment (the ASA test and perceptual-cue and task-requirement control tests) are shown schematically. Oblongs represent individual sound elements; for each element, width indicates relative duration. The vertical position of sound elements within each condition here is arbitrary and intended only to display the isochronous and anisochronous sequences. KEY: Pt, Target pitch, Pd, Distractor pitch. Sound examples are provided (numbers 84-89).

6.5.6 Test procedure

All sounds were presented as digital wavefiles from a notebook computer dichotically via Sennheiser HD 280-Pro headphones (Sennheiser, Wedeburg, Germany) at a sound pressure level of at least 70 dB. Each ASA assessment was administered in a fixed order: perceptual-cue control, task-requirement control, main test. Within each subtest, trials were presented in a fixed randomised order and response options were displayed in both verbal and diagrammatic form (see Figure 6.1 and Figure 6.2); responses could be made either verbally or by pointing, and were recorded for off-line analysis. Subjects were familiarised with task requirements prior to each test (using example stimuli not administered during the subsequent assessment). No feedback

about performance was given during the assessment and no time limit was imposed on subject responses.

6.6 Analysis

6.6.1 General neuropsychological functions

For the majority of tests in the general neuropsychological assessment (Table 6.1), raw results were transformed into standardised (IQ or Z) scores based on published norms for subsequent analysis. For the Mini-Mental State Examination and for tests also completed by the experimental control group, scores were analysed in raw format. For each test, linear regression was used to investigate the association of group with performance, adjusted for age and gender where score standardization had not already accounted for these factors.

6.6.2 Peripheral hearing

To examine the association of group with hearing, separate linear regression analyses were conducted for each of the frequency levels tested, adjusted for age and gender.

6.6.3 ASA assessments

Linear regression models were used to investigate the association of scores for each ASA test with group (control, AD). Separate models were evaluated for each auditory test, adjusted for age, gender and performance on the relevant perceptual-cue control test (Model 1). Three further models also included a general neuropsychological measure that was anticipated to contribute to ASA performance as an additional covariate: reverse digit span indexing auditory working memory (raw total score; Model 2), reverse visuo-spatial span indexing non-verbal working memory (raw total score; Model 3), and reaction time, indexing a combination of sustained and selective attention ('sustained plus selective' score; Model 4; see chapter appendix for further details).

An ASA discrepancy score (defined as score in the main ASA-grouping test minus score in the main ASA-segregation test) was calculated for each subject, in order to examine individual performance patterns. Finally, correlation analyses (Pearson's rho) within the AD group only were used in order to

assess: (i) the relation between performance on the two ASA main tests; (ii) the relation between performance on each of the ASA main tests and background neuropsychological and clinical measures.

6.6.4 General statistical methods

Owing to the relatively small group numbers in the study and large numbers of subjects performing at the test maxima, in general data did not meet normality assumptions. Therefore statistical inferences were made using bootstrapped confidence intervals (95% CIs, bias-corrected, accelerated with 2000 replications).

6.7 Results

6.7.1 General neuropsychological functions

The AD group was mildly to moderately impaired (performance above the 5th percentile but below the 10th percentile) on measures of performance IQ, verbal and visual recognition memory, and executive function (Table 6.1). On all tests performed both by the AD group and the healthy control group (digit span, visuo-spatial span, reaction time), patients performed significantly worse than controls (Table 6.1, all $p<0.05$).

6.7.2 Peripheral hearing

Sound detection thresholds for four of the five frequency levels examined (0.5, 2, 3, 4 kHz) did not differ between the AD and control groups (see chapter appendix, Table 6.5). Detection threshold in the AD group with respect to controls was raised at 1kHz; however this rise was small (equivalent to a mean intensity increase of approximately 5 dB). Overall, these results suggest that peripheral hearing was similar between the AD and healthy control groups.

6.7.3 ASA assessments

Raw data for the experimental auditory tests are displayed in Figure 6.3. Auditory performance data for each test are summarised in Table 6.2. The association of ASA scores (for each test separately) with the factor of group and a subset of neuropsychological measures (digit span, visual-spatial span, and reaction time) are presented in Table 6.3. Correlations between ASA

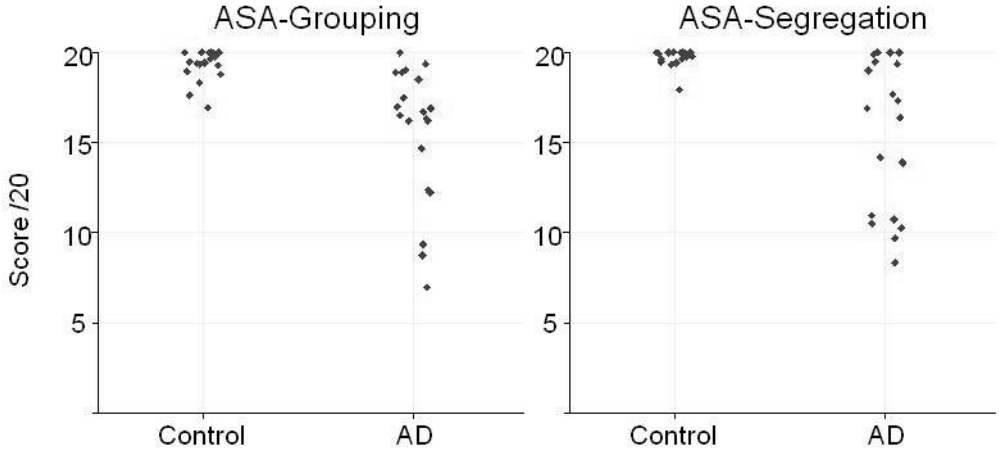
performance and other measures in the AD group are presented in Table 6.4. Figure 6.4 presents data on performance discrepancies between the two ASA tests in AD patients and controls. One AD patient failed to complete the ASA-segregation test due to time constraints; all other tests were completed by all subjects.

Table 6.2 ASA summary statistics: AD patients and healthy controls

Test	Task requirement control test (/10)		Perceptual cue control test (/10)		Main ASA test (/ 20)	
	AD	Control	AD	Control	AD	Control
	mean (std. dev.), minimum					
ASA-segregation*	10.0 (0.0), 10	10.0 (0.0), 10	9.4 (1.0), 7	10.0 (0.0), 10	15.5 (4.2), 9	19.9 (0.5), 18
ASA-grouping	10.0 (0.0), 10	10.0 (0.0), 10	9.9 (0.5), 8	10.0 (0.0), 10	15.7 (3.8), 7	19.4 (0.9), 17

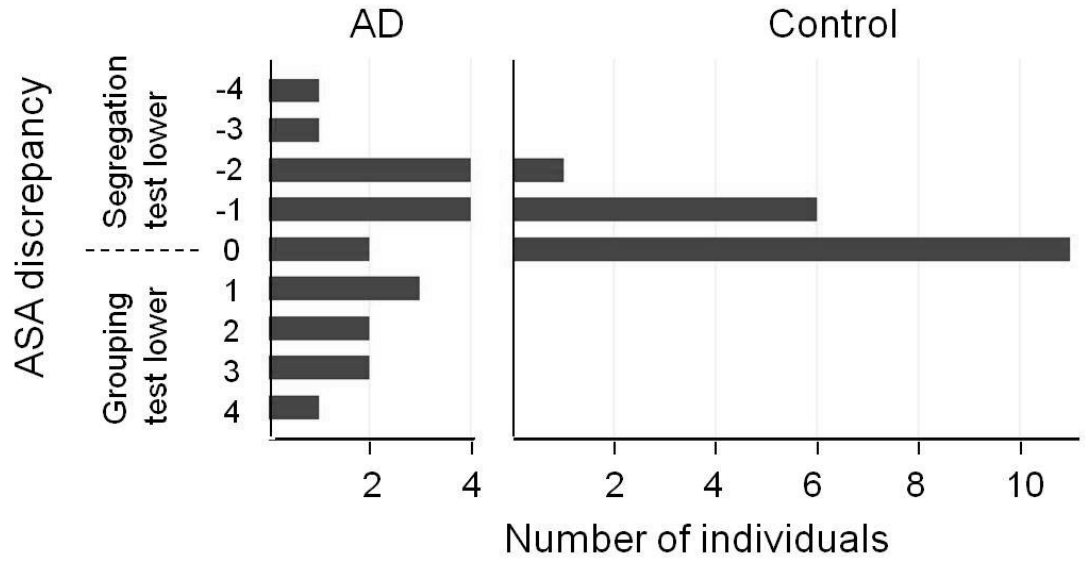
KEY: AD, Alzheimer's disease; *, N for the AD group was 20 rather than 21 (1 patient failed to complete this test); std. dev., standard deviation.

Figure 6.3 Raw ASA data: AD patients and healthy controls



KEY: AD, Alzheimer's Disease.

Figure 6.4 Frequency of ASA discrepancy scores: AD patients and healthy controls



KEY: AD, Alzheimer's disease; ASA discrepancy, score in the main ASA-grouping test minus score in the main ASA-segregation test.

Table 6.3 Association of ASA scores with group and neuropsychological measures

Model	ASA Test	Model covariates	Mean diff. in ASA test score (AD-C)	95% CI		Covariate	Mean change in ASA test score for one unit increase in covariate	95% CI	
				Lower	Upper			Lower	Upper
1	Seg	**group, age, gender, control test**	**-3.3**	-6.0	-1.6	**control test**	**2.0**	0.5	3.2
	Group		**-3.7**	-5.9	-2.2	**control test**	1.7	-2.7	4
2	Seg	**group, age, gender, control test, DS-R**	**-2.6**	-4.8	-1.1	**DS-R**	**0.3**	0.0	0.7
	Group		**-2.8**	-4.8	-1.1	**DS-R**	**0.4**	0.1	0.8
3	Seg	**group, age, gender, control test, VS-R**	-1.7	-5.7	0.0	**VS-R**	0.6	-0.3	1.5
	Group		-1.0	-2.9	1.2	**VS-R**	**0.9**	0.2	1.6
4	Seg	**group, age, gender, control test, RT-Sel.**	**-1.7**	-3.5	-0.3	**RT-Sel.**	**0.0**	0.0	0.0
	Group		**-2.6**	-5.2	-1.0	**RT-Sel.**	0.0	0.0	0.0

Effects with $p<0.05$ (inferred from bootstrapped confidence intervals) are shown in bold. Effects of covariates are assumed constant across groups (no interaction terms fitted). KEY: AD, Alzheimer's disease; C, control; CI, confidence interval (bootstrapped with bias-correction, acceleration and 2000 replications); DS-R, Digit span reverse; Group, ASA-grouping test; RT-Sel., reaction time test, 'sustained plus selective' score (see chapter appendix); Seg, ASA-segregation test; VS-R, visuo-spatial span reverse.

Table 6.4 Correlations between ASA performance and other measures in the AD group

	ASA-grouping	ASA-segregation
	Pearson's r (95% CI)	
ASA-segregation	**0.68 (0.40 to 0.86)**	-
MMSE	0.43 (-0.13 to 0.78)	0.41 (-0.21 to 0.77)
Disease duration	0.03 (-0.38 to 0.38)	0.03 (-0.31 to 0.37)
WASI VIQ	0.23 (-0.23 to 0.61)	0.26 (-0.20 to 0.62)
WASI PIQ	0.30 (-0.26 to 0.65)	0.38 (-0.10 to 0.69)
Dual num. canc. (total)	**0.52 (0.07 to 0.77)**	0.43 (-0.07 to 0.74)
DS-F	**0.51 (0.02 to 0.78)**	**0.54 (0.23 to 0.74)**
DS-R	0.48 (-0.06 to 0.74)	**0.59 (0.18 to 0.80)**
VS-F	0.35 (-0.21 to 0.72)	**0.57 (0.15 to 0.81)**
VS-R	**0.58 (0.14 to 0.85)**	**0.58 (0.00 to 0.84)**
RT-Sust.	-0.42 (-0.82 to 0.20)	**-0.46 (-0.73 to -0.10)**
RT-Sel.	-0.44 (-0.75 to 0.02)	**-0.76 (-0.87 to -0.51)**
Synonyms Concrete	-0.07 (-0.40 to 0.23)	-0.03 (-0.42 to 0.50)
Synonyms Abstract	-0.11 (-0.39 to 0.19)	-0.12 (-0.48 to 0.25)
BPVS	-0.05 (-0.29 to 0.17)	-0.04 (-0.37 to 0.26)
RMT Words	0.33 (-0.04 to 0.63)	0.30 (-0.17 to 0.62)
RMT Faces	0.24 (-0.10 to 0.57)	**0.61 (0.30 to 0.80)**
Object decision	0.30 (-0.13 to 0.62)	0.35 (-0.15 to 0.69)

Pearson's r correlations are presented with 95% confidence intervals (CIs; bootstrapped with bias-correction, acceleration and 2000 replications). Significant correlations ($p<0.05$, inferred from the CIs) are in bold. KEY: BPVS, British Picture Vocabulary Scale; DS-F/R, digit span forwards/reverse; Dual. num. canc., dual number cancellation; MMSE, Mini-Mental State Examination score; PIQ, performance IQ; RMT, Recognition Memory Test; RT-Sust./Sel., reaction time test 'sustained'/'sustained plus selective' score; (see chapter appendix); VS-F/R., visuo-spatial span forwards/reverse; VIQ, verbal IQ; WASI, Wechsler Abbreviated Scale of Intelligence.

The AD group showed deficits relative to the healthy control group on both the ASA-segregation and ASA-grouping tests (Table 6.3), though there was a wide spread of performance within the patient cohort (Figure 6.3). The magnitude of the deficit and the range of performance within the AD group was similar for both the ASA-segregation and ASA-grouping tests. For each ASA test, there was strong evidence for a difference in performance on ASA tests between controls and AD patients after adjusting for age, gender, control (perceptual-cue) test performance (Model 1). Further adjustment for auditory verbal working memory or sustained/selective attention did not substantially alter this result (Models 2 and 4; Table 6.3). However, adjustment for non-verbal (visuo-spatial) working memory performance (Model 3) explained some of the difference between controls and AD patients, with no evidence for a group difference on the ASA-grouping test after adjustment for this measure.

Several test pairings showed significant correlations within the AD group. Firstly, performance on the ASA-segregation and ASA-grouping tests was correlated (Table 6.4). Secondly, performance on each of the ASA tests was correlated with performance on general executive and attentional measures (auditory verbal and visuo-spatial span, reaction time, number cancellation). In addition, AD group performance on the ASA segregation test was correlated with recognition memory for faces. There was no evidence for an association of ASA performance with disease duration or global cognitive performance (Mini-Mental State Examination score).

The pattern of ASA test discrepancy scores amongst subjects differed for the AD and control groups (Figure 6.4). Most control subjects showed either no ASA discrepancy or a small discrepancy, whereas AD patients showed a spread of ASA discrepancy scores. Additionally, AD patients showed a similar frequency of discrepancies favouring either the ASA-segregation or the ASA-grouping test whereas control subjects showed discrepancies favouring only the ASA-grouping test, suggesting qualitatively different performance profiles at an individual level. Despite these trends, statistical analysis provided no evidence for a group difference in ASA discrepancy (Mann-Whitney U test, $p=0.8$). Each of the above findings are limited by the near-ceiling performance of controls, and thus a further analysis was used to determine whether overall ASA

performance level was related to ASA discrepancy within the AD group only. A non-parametric (Spearman's rank) correlation between ASA discrepancy score and mean ASA score (0.5* ASA-grouping score plus ASA-segregation score) was carried out; however, no evidence of a relationship was found (p=0.4).

6.8 Discussion

6.8.1 The cognitive basis of ASA deficits in AD

Here we have demonstrated that clinically typical AD is associated with ASA impairments. Previous evidence has suggested similar deficits in the auditory verbal modality (Gates et al., 1996; Gates et al., 2002; Gates et al., 2008); however, current evidence indicates that AD involves a primary non-verbal ASA impairment affecting sounds of all types. Impairments observed in this study were not accounted for by disease severity (duration), task-related factors, or basic auditory perceptual processes, and were only partly explained by executive performance; they are therefore likely to reflect relatively specific deficits of bottom-up and/or top-down ASA mechanisms (although this preliminary study was not designed to enable a more detailed cognitive characterisation of impairments). Additionally, the similar patterns of performance exhibited by the AD group across the two ASA tests (auditory object segregation and grouping), which on a priori grounds were likely to be differentially dependent upon general executive functions, provides further support for this conclusion. However, ASA scores were also partially influenced by non-verbal working memory capacity and correlated with performance on other executive measures. Thus, overall findings suggest that ASA may involve multiple relatively independent sub-processes, including both auditory-specific (bottom-up and top-down), and executive mechanisms. Additionally, current evidence for associations between these sub-processes indicate that they may exhibit close interdependencies within a distributed cortical network, in accord with studies of healthy control subjects (Schönwiesner et al., 2007; Overath et al., 2009); this conclusion gains particular support from previous evidence that AD involves damage to a functionally coherent but anatomically distributed cortical network (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010).

6.8.2 The anatomical basis of ASA deficits in AD

The development of ASA deficits in AD is consistent with the known topography of cortical pathology in this disease. Previous functional imaging work has shown that the temporo-parietal junction and adjacent auditory cortices are specifically engaged during ASA tasks (Deike et al., 2004; Cusack et al., 2005; Schönwiesner et al., 2007; Snyder and Alain, 2007; Gutschalk et al., 2007; Wilson et al., 2007; Deike et al., 2010; Schadwinkel and Gutschalk, 2010; Smith et al., 2010). Further, it has been proposed that association cortical areas of the posterior temporal lobe, such as the planum temporale, are likely to mediate top-down ASA mechanisms for matching incoming sound mixtures to stored auditory templates (Griffiths and Warren, 2002; Deike et al., 2004; Gutschalk et al., 2007; Wilson et al., 2007; Overath et al., 2009; Deike et al., 2010; Smith et al., 2010). In AD, there is prominent macroanatomical involvement of temporo-parietal cortices (Buckner et al., 2009; Zhou et al., 2010), while micro-anatomically, the pathological process particularly targets association cortex and synaptic trees (Baloyannis, 2009). The characteristic anatomical signature of AD therefore includes brain regions strongly implicated in ASA. Moreover, AD is associated with early and relatively selective damage to a 'default mode' cerebral network (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010) which is particularly active during internally directed cognitive tasks including remembering autobiographical details (episodic memory; Buckner et al., 2008), and imagining scenarios and visual scenes (Buckner et al., 2008; Hassabis and Maguire, 2007). Thus, the current evidence may tentatively suggest that this network also contributes to analogous functions in the auditory modality, including the storage and retrieval of auditory memories (i.e., auditory templates), and the representation of auditory scenes. Taken together, current work indicates that distributed damage in AD may overlap with a cortical network for ASA, potentially encompassing areas involved in bottom-up, top-down and executive sub-processes.

6.8.3 The involvement of memory processes in ASA

AD was associated here with deficits of both working and episodic memory, in accordance with previous findings (Rochon et al., 2000; Moss et al., 1986; Coen et al., 1997); thus, current evidence may suggest a close association between processes of memory and ASA. In support of this notion, ASA performance in

the AD group here correlated with auditory verbal and visuo-spatial working memory capacity, as well as with non-verbal episodic (face) memory. Further, although non-significant, the trend for AD patients (but not controls) to perform more poorly on the ASA grouping than the ASA segregation test (Figure 6.4) might reflect the effects of working memory deficits: grouping processes are likely to be particularly dependent on the tracking of auditory information over time (Bregman, 1990). Whilst the cognitive mechanisms and anatomical substrates that mediate non-verbal auditory memory (whether working or episodic) have not been fully defined, available evidence suggests that they are at least partially shared with analogous processes in other modalities (working memory: Klemen et al., 2009; Koelsch et al., 2009; Protzner et al., 2009; Schulze et al., 2010; episodic memory: Mohedano-Moriano et al., 2008; Henson and Gagnepain, 2010; Salami et al., 2010). However, further studies indicate that auditory memory mechanisms may show a degree of modality-specificity (Alain et al., 2008; Koelsch et al., 2009; Munoz-Lopez et al., 2010; Salami et al., 2010; Schulze et al., 2010; Schulze et al., 2011). Thus, further work is required both to delineate the memory systems implicated in non-verbal auditory processing, and the extent to which they interact with ASA processes.

6.8.4 The clinical implications of findings

Clinically, the characterisation of ASA deficits provides a basis for recognising and understanding an important class of symptoms in AD. In patients' daily lives, such symptoms might manifest as difficulty understanding and following speech, particularly in the presence of extraneous noise, but would also affect the detection, recognition and tracking of other kinds of complex sounds (for example, environmental noises or music). Owing to a lack of previous research, it is likely that these auditory cognitive symptoms are commonly under-recognised and perhaps ascribed to impairments of memory, attention or peripheral hearing. However, present evidence suggests that the routine assessment of ASA might ultimately aid the diagnosis of AD, thus enabling more effective plans for clinical management and, where available, pharmacological treatment. Additionally, since non-verbal auditory processing deficits are likely to arise in the early stages of AD (Gates et al., 1996; Gates et al., 2002; Gates et al,. 2008; Golob et al., 2007; Golob et al., 2009), ASA measures might potentially assist the prognosis of individuals with mild

cognitive impairment. Finally, whilst it is unlikely that ASA deficits would benefit from specific auditory treatments (such as amplification via hearing aids), symptoms might be managed by improved awareness and modification of the acoustic environment (e.g., patients might prefer to arrange social gatherings in quiet locations with minimal levels of background noise).

6.8.5 Summary of results and suggestions for further work

Current evidence suggests that ASA deficits in AD reflect the impairment of multiple relatively independent cognitive processes, including both auditory-specific (bottom-up and top-down) and executive mechanisms. Moreover, such findings suggest that corresponding processes may be relatively dissociable in the healthy brain. However, observed associations between these auditory-specific and executive mechanisms, together with studies showing that AD involves damage to wide-spread but functionally coherent brain regions (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010), lead to the additional suggestion that sub-processes of ASA may be closely interrelated. Together, these data indicate that ASA involves multiple cognitive processes with varying degrees of cognitive independence, and is likely mediated by a network of distributed regions with varying levels of functional specialisation; such conclusions are in accordance with previous neuroimaging studies of healthy controls (e.g., Deike et al., 2004; Schönwiesner et al., 2007; Wilson et al., 2007; Overath et al., 2009; Deike et al., 2010). However, the findings of this study are preliminary and will require corroboration and development in future studies. For example, the current study was not equipped to elucidate the specific cognitive locus of impairments, and future work will be required to characterise the cognitive and anatomical profiles of bottom-up, top-down and executive ASA mechanisms, and their interactions. Similarly, further work is also required to establish the relation between processes of ASA and other cognitive functions including working and episodic memory. An adequate exploration of these issues will require both neuroimaging and neuropsychological studies, as well as paradigms involving the systematic manipulation of multiple stimulus parameters (e.g., acoustic properties, sound categories, contextual and attentional factors). Further, such studies should utilise structural and functional connectivity methods to delineate the distributed neural networks that are likely to mediate ASA. Finally, in order

to realise the clinical potential of findings, future work should address the specificity of the ASA disorder for AD versus other dementias, and the longitudinal evolution of auditory dysfunction in relation to other symptoms.

6.9 Chapter appendix

6.9.1 Reaction Time test

The reaction time test was adapted from Stuss et al. (2005), and was designed to measure sustained and selective (visual) attention. The task had two conditions: a ‘sustained’ condition in which subjects were required to attend and respond to stimuli presented over a period of time according to pre-specified instructions; and a ‘sustained plus selective’ condition in which subjects were required to respond in the same way, but only for certain subtypes of stimuli. Stimuli were upper case letters presented against a fixed plain background on a notebook computer screen using COGENT 2000 (www.vislab.ucl.ac.uk/cogent_2000.php), run under MATLAB (MathWorks™). The ‘sustained’ condition comprised 10 presentations of the letter ‘X’; subjects were instructed to watch the screen and press a response button upon seeing the letter ‘X’. The ‘sustained plus selective’ condition comprised 10 presentations of the letter ‘X’ and 10 presentations of the letter ‘O’ in a fixed random order; subjects were instructed to press the response button upon seeing the letter ‘X’, but not the letter ‘O’. In both conditions, inter-stimulus interval was varied randomly between 800 and 5000ms. All subjects completed the sustained condition followed by the sustained plus selective condition consecutively; subjects were familiarised with the task prior to each condition. In both conditions, reaction time (RT) was measured as the latency between stimulus onset and button press response. Within each condition, RTs were averaged to give a ‘sustained’ and a ‘sustained plus selective’ score for each subject.

Table 6.5 Sound detection thresholds in AD group vs. healthy controls

Frequency (kHz)	Mean group difference (s)	95% CI (s)	
		Lower	Upper
0.5	2.7	-0.8	6.3
1	**3.8**	1.4	5.8
2	3.1	-0.8	7.8
3	0.5	-4.4	5.8
4	5.8	-3	13.6

Bold numbers indicate a significant difference between patient and control groups, inferred from bootstrapped confidence intervals ($p<0.05$). Positive differences indicate that AD patients showed higher thresholds. KEY: AD, Alzheimer's disease; CI, confidence interval (bootstrapped with bias-correction, acceleration and 2000 replications).

7 Discussion

This thesis has presented a series of studies into the neuropsychology of non-verbal auditory processing in dementia. In the past, little work has been conducted in this area, owing to a range of problems traversing conceptual and practical issues (e.g., the definition of auditory objects, see section 1.2; the construction of auditory neuropsychological tests, see section 2.3). Although the results of current investigations are preliminary, they suggest certain key directions for future work. In particular, insights provided have implications for two distinct but closely related fields of inquiry: the cognitive profiles (or 'signatures') of various dementia syndromes, and the architecture of non-verbal auditory processing in the healthy brain. This final chapter will proceed by summarising the results of this thesis in relation to each of these perspectives separately.

7.1 The non-verbal auditory cognitive signatures of dementia syndromes

The findings of this thesis have added weight to the neuropsychological literature of non-verbal auditory processing deficits in dementia (Rapcsak et al., 1989; Kurylo et al., 1993; Eustache et al., 1995; Gates et al,. 1996; Hellstrom and Almkvist, 1997; Otsuki et al., 1998; Bozeat et al., 2000; Gates et al,. 2002; Kuramoto et al., 2002; Gainotti et al., 2003; Uttner et al., 2006; Iizuka et al., 2007; Gates et al., 2008; Jorgens et al., 2008; Baird et al., 2009; Hailstone et al., 2009; Jeon et al., 2009; Omar et al., 2010; Vanstone et al., 2010). Whilst further investigations will be required in larger patient cohorts, current findings suggest that different dementia syndromes lead to distinct profiles, or 'signatures', of non-verbal auditory processing impairment. Furthermore, for each of the dementia syndromes examined, results allow the preliminary specification of such signatures as follows.

7.1.1 The non-verbal auditory processing signature of PNFA

The investigations of Chapters 2, 3 and 4 suggest that PNFA involves predominant impairments of auditory perceptual property processing. In particular, results emphasise deficits of timbre analysis (i.e., dystimbria), despite

preserved processing of more basic perceptual properties (e.g., loudness, pitch). Thus, patients may suffer selective impairments for representing complex spectral, temporal and spectrotemporal timbral properties that are likely to hold relevance to object processing. In particular, the description of Case 2 (Chapter 4) provided some insight into the cognitive basis of such deficits in PNFA: whilst dystimbria has been previously associated with various combinations of complex temporal, spectral and spectrotemporal impairments (e.g., Albert and Bear, 1974; Auerbach et al., 1982; Wang et al., 2000; Kohlmetz et al., 2003; Stefanatos et al., 2005; Griffiths et al., 2007), Case 2 exhibited both temporal and spectral deficits, but with a particularly severe impairment of temporal property processing. The findings of this thesis also suggest that PNFA leads to impairments during auditory apperceptive and semantic processing tasks. On the basis of current data alone it is not possible to establish whether the overall performance profile of PNFA reflects multiple independent deficits, or a primary dystimbria that gives rise to impairments at related cognitive stages. However, a range of previous literature suggests that auditory cognition involves the predominantly serial flow of information through increasingly complex stages of processing (Rauschecker et al., 1998; Binder et al., 2000; Wessinger et al., 2001; Griffiths and Warren, 2004). Additionally, whilst empirical evidence is limited, PNFA is not typically associated with deficits of apperceptive and semantic object processing in alternative modalities such as vision (Grossman and Ash, 2004; Bonner et al., 2010). Therefore, it may be suggested that auditory apperceptive and semantic impairments observed in PNFA are caused by the cascading effects of a primary dystimbria. Notably, this hypothesis aligns with anatomical evidence in PNFA, which emphasises structural and functional damage to a peri-Sylvian network implicated in non-verbal auditory property processing (Gorno-Tempini et al., 2004; Schroeter et al., 2007; Seeley et al., 2009; Hu et al., 2010; Rohrer et al., 2010b). Thus, the non-verbal auditory signature of PNFA may involve primary impairments of complex property processing, i.e., dystimbria, which additionally lead to secondary apperceptive and semantic impairments via bottom-up neural connections within a distributed network.

7.1.2 The non-verbal auditory processing signature of SD

The pan-modal object recognition impairments observed in SD (Chapters 2, 5) support previous assertions that this syndrome is characterised by an amodal semantic processing deficit in association with damage to the anterior temporal lobes (ATLs; e.g., Bozeat et al., 2000; Hodges and Patterson, 1996; Mayberry et al,. 2010). However, findings within this thesis indicate that SD also affects further cognitive processes and brain areas. For example, in behavioural testing (Chapter 2), SD patients exhibited parallel deficits in auditory apperceptive and semantic tasks. Additionally, during an fMRI study of auditory object processing (Chapter 5), disease-related activity during both perceptual and category-specific semantic processing traversed widespread temporal regions and extended into the inferior parietal lobe. Comparing this distribution of activity with previous work suggests not only an amodal semantic processing disorder, but also the involvement of perceptual (Wessinger et al., 2001) and multi-modal semantic (Lewis et al., 2005; Lewis et al., 2006; Pobric et al., 2010a) mechanisms. Furthermore, overlapping patterns of disease-related activity between conditions indicate a close coupling between perceptual and semantic stages of auditory processing. From an anatomical perspective, the results of Chapter 5 suggest the involvement of regions beyond the zone of maximal atrophy in the anterior temporal lobes, thus indicating functional in addition to structural abnormalities throughout temporo-parietal regions. Taken together, the findings of this thesis suggest that the non-verbal auditory processing signature of SD may involve damage to a common temporo-parietal brain network for perceptual, multi-modal semantic and amodal semantic stages of auditory object processing. From this perspective, disease-related activity observed in Chapter 5 might indicate a disruption of links between auditory perceptual and corresponding semantic representations that normally support mechanisms of sound recognition. Notably, these conclusions align with previous investigations of resting state connectivity in SD which demonstrate the dysfunction of a distributed but functionally coherent object recognition network (Seeley et al., 2009); importantly, the present fMRI data (Chapter 5) augment such findings by characterising network dysfunction in the working brain during auditory processing.

7.1.3 The non-verbal auditory processing signature of LPA

The results of Chapters 3 and 4 suggest that LPA may lead to generic deficits of non-verbal auditory perception that are underpinned, at least in part, by working memory impairments. Although working memory impairments have been emphasised in previous descriptions of LPA (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2011), current findings indicate that they extend beyond the verbal and visuo-spatial modalities to affect non-verbal auditory processing. However, the results of a detailed single case study (Case 1, Chapter 4) may indicate that LPA also involves specific deficits of non-verbal auditory perception. Although a precise characterisation of underlying auditory impairments was not possible (see section 4.8.2), observations of Case 1 may reflect selective damage to a network for processing relatively basic spectral and temporal auditory properties (e.g., pitch, loudness), which incorporates closely associated executive mechanisms required for tracking properties as they evolve over time (i.e., working memory). Alternatively, results might tentatively suggest the selective impairment of a putative system for matching incoming sounds to stored auditory representations or 'templates' (Warren and Griffiths, 2002), which would also incorporate intrinsic working memory mechanisms; this system is likely to provide key inputs during both auditory apperception and auditory scene analysis (ASA). Whichever interpretation is preferred, the observed profile of deficits aligns with descriptions of atrophy in LPA, which involve a predominantly left-sided peri-Sylvian network encompassing temporal and inferior parietal regions associated with both non-verbal auditory perceptual processing and working memory (Gorno-Tempini et al., 2004; Rohrer et al., 2010b). Taken together, present evidence suggests that the non-verbal auditory signature of LPA involves closely associated impairments of non-verbal auditory processing and working memory, resulting from damage to a functionally coherent temporo-parietal network.

7.1.4 The non-verbal auditory processing signature of AD

The results of Chapters 3 and 6 suggest that the non-verbal auditory processing signature of AD involves predominant deficits of apperception and auditory scene analysis (ASA). In particular, the emergence of equivalent deficits in two independent ASA tests (Chapter 6), in parallel with an apperceptive deficit (Chapter 3), might suggest the presence of a common underlying impairment

for the processing of preliminary auditory object representations, i.e., auditory templates (see section 1.5.3.6.2). Convergent evidence for this assertion is provided by previous neuropsychological evidence (involving verbal auditory stimuli; Gates et al,. 1996; Gates et al,. 2002; Gates et al., 2008), as well as the observation that AD patients commonly exhibit atrophy within temporo-parietal cortices including the planum temporale (Whitwell et al., 2005; Buckner et al., 2009; Zhou et al., 2010), which are implicated in auditory template processing (Griffiths and Warren, 2002; Deike et al., 2004; Gutschalk et al., 2007; Wilson et al., 2007; Overath et al., 2009; Smith et al., 2010; Deike et al., 2010; Schadwinkel and Gutschalk, 2010). However, non-auditory impairments might also contribute to ASA and apperceptive deficits in AD. For example, this disease typically involves predominant impairments of episodic memory which might conceivably disrupt the storage and retrieval of previously encountered auditory templates, in association with damage to a functionally coherent 'default network' (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010); however, the involvement of this network in non-verbal auditory processing remains to be established. Additionally, visual apperceptive impairments have been previously reported in AD subjects (Mendez et al., 1990; Uhlhaas et al., 2008), and it is possible that current findings can be at least partially accounted for by a modality-general apperceptive disorder (although the extent to which apperceptive mechanisms are shared between modalities has yet to be investigated). Taken together, present evidence suggests that the non-verbal auditory signature of AD involves both auditory-specific and non-auditory deficits that may lead to the predominant impairment of auditory template processing, in association with damage to a functionally coherent distributed neural network.

7.1.5 The non-verbal auditory cognitive signatures of dementia syndromes: clinical implications

Insight into the non-verbal auditory processing signatures of distinct dementia syndromes is likely to assist the clinical management of patients. For example, the characterisation of involved deficits provides a basis for recognising and understanding an important class of symptoms. In patients' daily lives, such symptoms might manifest as difficulty understanding and following speech, particularly in the presence of extraneous noise, but would also affect the

detection, recognition and tracking of other kinds of complex sounds (for example, environmental noises or music). However, owing to a lack of previous research, it is likely that these auditory cognitive symptoms are commonly under-recognised and perhaps ascribed to impairments of memory, attention or peripheral hearing. Notably, the evidence of this thesis suggests the potential utility of administering standardised non-verbal auditory cognitive assessments. Whilst the routine administration of comprehensive assessments like those described in this thesis is unlikely to be feasible, brief screening tests might provide a time-efficient means to gather preliminary diagnostic data. For example, auditory cognitive deficits could be eliminated from the diagnoses of patients showing normal levels of performance, whilst the administration of more comprehensive auditory assessments would be empirically justified in patients showing deficits. Additionally, results might assist the interpretation of routine neuropsychological tests that rely upon intact auditory perception. Ultimately, the assessment of non-verbal auditory cognition might aid the differentiation and diagnosis of dementia syndromes, thus providing increased information upon which to base plans for clinical management and, where available, pharmacological treatment. Particular benefits would follow where non-verbal auditory processing deficits arise at early stages of the disease process (e.g., ASA deficits in AD; Gates et al., 1996; Gates et al., 2002; Golob et al., 2007; Gates et al,. 2008; Golob et al., 2009), possibly facilitating earlier diagnosis. Additionally, whilst it is unlikely that non-verbal auditory processing disorders would benefit from specific auditory treatments (such as amplification via hearing aids), it is possible that symptoms might be managed by improved awareness and modification of the acoustic environment. For example, patients and carers might be advised, where possible, to arrange social gatherings in quiet locations (e.g., family dinners at home rather than in a busy restaurant). During conversation, carers might attempt to ensure that they speak clearly, and that the patient receives as much information as possible via non-verbal means (e.g., lip movements, body language, pointing). Additionally, preferred activities might be adapted so that they do not rely upon high levels of auditory perception: patients might enjoy films and television programmes that are primarily reliant upon visual information (silent or visually comic films; cookery, sport or nature programmes), and listening to (and singing) music with single, simple melody lines (e.g., traditional songs, hymns). Finally, the dissemination

of knowledge about non-verbal auditory processing disorders will help to increase awareness amongst relevant health professionals, charitable organisations, and carers, thus leading to further improvements in patient services.

7.1.6 The non-verbal auditory cognitive signatures of dementia syndromes: research implications

Insight into the non-verbal auditory processing signatures of distinct dementia syndromes is also likely to assist the scientific understanding of underlying disease mechanisms. For example, earlier or more accurate diagnoses enabled by the recognition of syndrome-specific signatures might allow patients to become involved in research sooner than would otherwise be possible, in particular providing greater scope for longitudinal experimental studies and clinical trials. Additionally, to the extent that mechanisms of non-verbal auditory processing involve the action of distributed cortical networks (Wessinger et al., 2001; Griffiths and Warren, 2002; Griffiths and Warren, 2004; Griffiths et al., 2007; Staeren et al., 2009; Peretz et al., 2009; Leaver and Rauschecker, 2010; Hyde et al., 2010), auditory measures may provide indices of network-level dysfunction and degeneration in dementia (Sonty et al., 2007; Buckner et al., 2009; Meslaum, 2009; Seeley et al., 2009; Zhou et al, 2010). In these ways, non-verbal auditory processing signatures hold potential to provide useful biomarkers for tracking disease progression and treatment efficacy in clinical studies. Ultimately, each of these research strategies should increase knowledge about the core cognitive and anatomical features of dementia syndromes, which, in turn, will lead to further improvements in patient care.

7.2 The cognitive architecture of non-verbal auditory processing

7.2.1 An introduction to the architecture of cognitive processing

Previously, numerous theoretical accounts of the general architecture of cortical cognitive processing (irrespective of modality) have been proposed; however, most theories can be located on a continuum extending between purely ‘componential’ and purely ‘distributed’ positions. Componential theories suggest

that cognition can be organised into a set of dissociable processes, each associated with a distinct anatomical substrate (Chomsky, 1980; Marr, 1982; Fodor, 1983; Coltheart, 1985; Shallice, 1988). Although different versions of componential theories attribute varying degrees of independence to components, all posit that the brain contains regions that show some degree of functional specialisation. In contrast, distributed theories suggest that cognitive processing takes place via the concerted activity of a large number of homogenous neuron-like processing units which are connected in large networks (Rumelhart et al., 1986; Farah and McClelland, 1991; Plaut and Shallice, 1993, Plaut, 1995). Whilst versions of distributed theories also vary, one strong implication is that the brain does not contain regions of functional specialisation; instead, cognitive processes show distributed and overlapping patterns of activity and are therefore interdependent. Much controversy has surrounded the debate between componential and distributed accounts of cognition. In particular, disputes have been fuelled by empirical investigations showing that double dissociations, which potentially offer the most powerful evidence for componential cognitive processes, may also emerge from distributed architectures (e.g., Plaut, 1995). Such findings question the assumption that there is any simple link between empirical neuropsychological data and the underlying architecture of cognition; however, since biological systems in general tend to show functional specialisation, it is more plausible that such a link would be highly complex rather than entirely absent (Shallice, 1988). Recently, theoretical advances have combined aspects of componential and distributed theories, suggesting that processes vary in the extent to which they show cognitive and anatomical independence (e.g., Op de Beeck et al., 2008). Within such theories, although certain cognitive processes are either totally componential or distributed, others may exist at an intermediate level. Such intermediate processes would show a degree of independence, but would also rely to some extent upon informational exchanges, or interdependencies, with other processes. From this perspective, states of cognitive independence and interdependence are not mutually exclusive, and could exist within the same cognitive architecture (Op de Beeck et al., 2008). In what follows, this moderate theoretical approach will be adopted, and available evidence will be used to characterise the various sub-processes of non-verbal auditory cognition

individually, focussing upon the degree to which each exhibits cognitive independence and/or interdependence.

7.2.2 Auditory perceptual property processing

The results of Chapters 2, 3 and 4 indicate that PNFA leads to range of non-verbal auditory processing deficits, affecting perceptual property, apperceptive and semantic stages of analysis; furthermore, the results of Chapter 3 suggest that these deficits show close associations with executive processing mechanisms. Nevertheless, Chapters 2, 3 and 4 provide convergent evidence, using different tasks and patient samples, for particularly severe impairments of auditory perceptual property processing in PNFA. On the basis of current data alone it is not possible to establish whether this performance pattern might reflect multiple independent deficits, or a primary perceptual property processing disorder that gives rise to impairments at related cognitive stages. However and as already argued (section 7.1.1), since non-verbal auditory processing proceeds in a predominantly serial fashion through increasingly complex stages of cognition, (Rauschecker et al., 1998; Wessinger et al., 2001; Griffiths and Warren, 2004), deficits in PNFA are likely to reflect the effects of an underlying perceptual property processing disorder. Additionally, since perceptual property deficits observed here in PNFA predominantly involved the analysis of complex spectral, temporal and spectrotemporal properties which are likely to be relevant to the formation of object representations (rather than more basic properties such as pitch and loudness), results indicate a core deficit of timbre processing, i.e., dystimbria. Thus, current data provide tentative evidence for the relatively selective impairment, and thus relative cognitive independence, of timbre processing. Additionally, the observation of dystimbria in PNFA, a neurodegenerative disease involving selective damage to functionally coherent brain regions (Seeley et al., 2009), may suggest that timbre processing is reliant upon network-level operations. Notably, this conclusion is supported by neuroimaging studies of healthy controls which describe timbre processing networks centred upon the superior temporal lobes (Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010; Kumar et al., 2007; Griffiths et al., 2007). Given that PNFA leads to prominent damage within similar cortical regions (Gorno-Tempini et al., 2004; Schroeter et al., 2007; Rohrer et al., 2009; Rohrer et al., 2010b; Hu et al., 2010), current

evidence may therefore indicate the action of a distributed superior temporal network for timbre analysis, which furthermore incorporates close links with both auditory object and executive processing mechanisms.

Additional insight into brain mechanisms of timbre processing is provided by the detailed examination of a single patient with PNFA. Case 2 (Chapter 4) showed impairments for processing complex spectral, temporal and spectrotemporal (timbral) properties that are likely to be relevant to the formation of object representations, despite preserved perception of more basic spectral and temporal properties (pitch, loudness). Moreover, detailed psychoacoustic assessments involving spectrotemporal object stimuli revealed deficits of both complex spectral and temporal property processing, but with a particularly severe impairment of temporal property processing. It can therefore be suggested that this patient exhibited a dystimbria syndrome affecting the representation of complex spectral, temporal and spectrotemporal object information, but with disproportionate deficits in the fine-grained analysis of temporal changes. Case 2 showed bilateral but predominantly left-sided frontotemporal atrophy with particular involvement of the left superior temporal lobe; on the basis of previous neuroimaging evidence (Zatorre and Belin, 2001; Schönwiesner et al., 2005; Altmann et al., 2010), this leftward bias of cortical damage may account for the predominance of temporal over spectral deficits. Finally, Case 2 also showed relatively severe deficits of auditory object (apperceptive and semantic) cognition, which might indicate a close association between mechanisms of timbre analysis and object processing. Taken together, Case 2 provides further neuropsychological evidence for a distributed timbre processing network centred upon the superior temporal lobes, which additionally exhibits important interactions with related stages of auditory cognition (e.g., object processing).

Although the most common property analysis deficit found in current investigations was dystimbria, a further single case (Case 1, Chapter 4) exhibited relatively preserved timbre processing alongside impairments for a distinct stage of property processing. Although Case 1's performance may be explained in different ways (see section 4.8.1), observations might signal the disease-modulation of mechanisms for the analysis of relatively basic auditory

properties including pitch and loudness. Further, these deficits in Case 1 exhibited a degree of property-specificity, and also showed a close association with executive processes necessary for tracking properties as they evolve over time (i.e., working memory). Notably, previous neuroimaging studies describe distributed auditory property processing networks that operate in a property-specific manner, and incorporate superior temporal and inferior parietal regions associated with both perceptual and executive mechanisms (e.g., Schulze et al., 2010; Schulze et al., 2011; Hyde et al., 2006; Hyde et al., 2007; Peretz et al., 2009; Hyde et al., 2010); moreover, atrophy in Case 1 overlapped with these networks. Additionally, previous studies indicate that PPA leads to network-level cortical damage (Seeley et al., 2009). Thus, current evidence may suggest the action of a relatively independent distributed network for processing basic auditory properties, which furthermore incorporates both property-specific and working memory mechanisms.

Taken together, both previous and current evidence suggest that different auditory properties may be processed within overlapping but functionally separable distributed networks centred upon the superior temporal lobes. In particular, Cases 1 and 2 provide evidence for a double dissociation between mechanisms for processing relatively basic perceptual properties that do not necessarily constitute whole objects (pitch, loudness), and more complex perceptual properties that are likely to contribute to whole object representations (timbre); whilst both sub-stages of property analysis are likely to involve the processing of spectral and/or temporal information, object-relevant stages are likely to involve the analysis of more complex spectral, temporal and additionally spectrotemporal structure. Additionally, both Cases 1 and 2 indicate important dependencies between auditory property analysis and other closely related processes (e.g., auditory object representation, executive processing). Notably, previous neuropsychological evidence suggests that auditory property perception may be divisible into relatively independent spectral, temporal and spectrotemporal processing sub-stages (Lechevalier et al., 1984; Tanaka et al., 1987; Zatorre, 1988; Johnsrude et al., 2000; Zatorre and Belin, 2001; Patterson et al., 2002; Tramo et al., 2002; Kohlmetz et al. 2003; Poeppel et al., 2003; Gutschalk et al., 2004; Penagos et al., 2004; Boemio et al., 2005; Schneider et al., 2005; Schönwiesner et al., 2005; Terao et al., 2005; Griffiths et al., 2007;

Altman et al., 2010). At the same time, neuroimaging studies of healthy controls describe a distributed superior temporal property processing network showing graded topographical organisation of spectral, temporal and spectrotemporal representations, thus emphasising interdependencies between these processing sub-stages (Zatorre and Belin, 2001; Poeppel, 2003; Boemio et al., 2005; Schönwiesner et al., 2005; Altman et al., 2010; Kumar et al., 2007; Griffiths et al., 2007). Further, although links between these sub-stages remain to be established, indirect sources of cognitive (Wessinger et al., 2001; Griffiths and Warren, 2004) and anatomical (Kaas and Hackett, 2000) evidence suggest that the outputs of basic spectral and temporal processes might combine to facilitate the subsequent generation of more complex spectral, temporal and spectrotemporal representations in posterior temporal regions (Altman et al., 2010). Taken together, this evidence indicates that auditory property perception is unlikely to be a unitary stage of cognition, and may consist of several sub-stages that show relative cognitive independence, but also close interdependencies with both one another and further cognitive processes (e.g., auditory object representation, executive processing); moreover, such mechanisms are likely to be instantiated within a distributed superior temporal network containing regions showing functional specialisation for particular sub-stages of processing.

7.2.3 Auditory apperception and auditory scene analysis

As described in the introduction (section 1.5.3.1), the existence of a discrete stage of apperception in the auditory modality remains a matter of debate. Previous neuropsychological studies provide limited evidence for a dissociation between apperceptive and semantic stages of auditory processing (Mendez and Geehan, 1988; Eustache et al., 1990; Fujii et al., 1990; Schnider et al., 1994; Habib et al., 1995; Vignolo, 2003). Further, the single case literature describes patients with predominant apperceptive deficits; however, these are often accompanied by particular combinations of more basic property processing deficits. Nevertheless, since accompanying property processing deficits in a subset of cases affect only restricted parameter ranges and cause disproportionate deficits of object processing within circumscribed sound categories (e.g., Fujii et al., 1990; Habib et al., 1995; Griffiths et al., 1997; Wang et al., 2000; Saygin et al., 2010), it can be argued that such patients suffer

predominantly apperceptive disorders. However, a clear anatomical substrate for auditory apperceptive deficits has yet to be established, although patients tend to show cortical damage within primary and/or association auditory cortices bilaterally, and their connections (Griffiths et al., 1999). Thus, previous data provide some support for the existence of selective auditory apperceptive deficits, but suggest that they may be less selective than analogous disorders in the visual modality, and more dependent upon other processes such as property perception.

Throughout the studies of this thesis, apperceptive deficits were observed within PNFA, SD, LPA and AD patient groups. However, these deficits were often accompanied by more severe perceptual property or semantic processing deficits (Chapters 2, 3, 4); such observations suggest that the majority of apperceptive impairments observed here reflect the secondary effects of primary disorders for other stages of non-verbal processing. However, the evidence of Chapter 3 may indicate a relatively selective deficit of auditory apperception in patients with AD. Specifically, whilst the AD group in this study exhibited a variety of auditory impairments, they showed disproportionately severe apperceptive impairments. As before, it is not possible to determine whether this behavioural profile reflects multiple independent deficits, or a single primary apperceptive disorder that gives rise to deficits at related processing stages. However, the observation of disproportionate apperceptive deficits in parallel with other less prominent impairments may tentatively suggest that auditory apperception exhibits both a degree of cognitive independence, as well as interdependencies with other auditory (and non-auditory) processes. Further, such conclusions indicate that auditory apperception may rely upon the action of a distributed neural network. Notably, this conclusion is supported both by previous studies showing that AD involves damage to large but functionally coherent cortical networks (Buckner et al., 2005; Buckner et al., 2009; Seeley et al., 2009; Zhou et al., 2010), and descriptions of auditory object processing networks in healthy controls (e.g., Staeren et al., 2009; Leaver and Rauschecker, 2010). Further, although the direction of interdependencies within this putative network is not established by current data, associations with both simpler (perceptual property) and more complex (semantic) stages of cognition may suggest that information flows in both bottom-up and top-down directions.

More detailed insight into the nature of the auditory apperceptive disorder in AD is provided by the conjunction of results from Chapters 3 and 6. In these studies, which were conducted in near identical AD groups, patients exhibited apperceptive impairments (Chapter 3) in addition to equivalent deficits in two independent auditory scene analysis (ASA) tests (Chapter 6). It can be suggested that this pattern of performance might indicate an underlying impairment of 'auditory template' matching (see section 1.5.3.6.2). Specifically, such an impairment would affect both processes of auditory object invariance required for apperception (section 1.5.3.1), and the parsing of auditory scenes on the basis of prior stored knowledge (top-down ASA mechanisms; section 1.5.4.3.2). Notably, the characteristic anatomical signature of AD (Gates et al,. 1996; Gates et al,. 2002; Whitwell et al., 2005; Gates et al., 2008; Buckner et al., 2009; Zhou et al., 2010) includes temporo-parietal and inferior frontal regions of the dorsal auditory pathway that are strongly implicated in distributed networks for template processing (Griffiths and Warren, 2002; Deike et al., 2004; Wilson et al., 2007; Gutschalk et al., 2007; Overath et al., 2009; Deike et al., 2010; Schadwinkel and Gutschalk, 2010; Smith et al., 2010). Thus, current data may provide important neuropsychological evidence for the relative cognitive independence of auditory apperception, or auditory template processing, in association with a distributed network traversing regions of the dorsal auditory pathway.

Additionally, although various accounts of Case 1's performance (Chapter 4) can be offered (see section 4.8.1), her cognitive profile might tentatively provide further evidence for a relatively independent stage of auditory template processing. Specifically, this patient showed greater impairments during tasks that were likely to impose high computational loads upon the putative auditory template matching system. For example, sound objects that contain few object-specific properties (e.g., loudness) are less likely than those that contain many (e.g., certain types of pitch, timbre) to correspond to a particular stored auditory template, and may therefore impose a higher computational load upon the template matching system. Here, Case 1's performance aligned with these factors: she exhibited a severe impairment of loudness perception, a more restricted impairment of pitch perception, and normal timbre perception.

Additionally, the template matching system is likely to be taxed more heavily during the processing of multiple compared to single objects; indeed, Case 1 showed particular impairments during the processing of multi-object stimuli. Thus, current data may indicate selective damage to an auditory template matching system in Case 1, which might manifest as a reduction in processing capacity. Furthermore, brain damage in PPA is likely to involve the selective degeneration of a functionally coherent network (Seeley et al., 2009), and the atrophy pattern exhibited by Case 1 incorporated temporo-parietal and inferior frontal regions that are strongly implicated in template processing (Griffiths and Warren, 2002; Deike et al., 2004; Wilson et al., 2007; Gutschalk et al., 2007; Overath et al., 2009; Deike et al., 2010; Schadwinkel and Gutschalk, 2010; Smith et al., 2010). Thus, in line with previous theoretical accounts (e.g., Griffiths and Warren, 2002; Warren et al., 2005), Case 1 might provide neuropsychological evidence for a relatively independent auditory template matching system in association with a distributed temporal-parietal network.

Despite these findings, evidence for an independent stage of auditory apperception, both within this thesis and previous neuropsychological literature, is limited. However, relevant neuroimaging studies may offer some helpful insights. In particular, as described in the introduction (section 1.5.3.6), they indicate that auditory apperception may be divisible into multiple processing stages. Firstly, sub-regions of the auditory cortices show functional specialization for the processing of different spectral, temporal and spectrotemporal properties (or processing within longer and shorter time windows; Giraud et al., 2000; Zatorre and Belin, 2001; Poeppel, 2003; Boemio et al., 2005; Schönwiesner et al., 2005; Altmann et al., 2010); thus, object-specific property combinations may elicit object-specific profiles of auditory cortical activity which provide key inputs for subsequent apperceptive processes. Secondly, the planum temporale (in auditory association cortices), may generate initial apperceptive representations via a process of matching incoming information to stored auditory templates (Griffiths and Warren, 2002; Deike et al., 2004; Gutschalk et al., 2007; Wilson et al., 2007; Overath et al., 2009; Deike et al., 2010; Schadwinkel and Gutschalk, 2010; Smith et al., 2010). Lastly, it is likely that anterior and ventral regions of auditory association cortices are implicated in generating fully elaborated apperceptive

representations that may facilitate sound recognition and ultimately guide behaviour (Scott et al., 2000; Belin et al., 2000; Belin et al., 2002; Belin and Zatorre, 2003; Warren et al., 2006; Leaver and Rauschecker, 2010). Whilst both current and previous data suggest that auditory template processing in the planum temporale shows a degree of cognitive independence (Griffiths and Warren, 2002), other sub-stages of apperceptive processing are likely to show greater dependence upon further cognitive processes, including perceptual property and semantic mechanisms. Such indications may account for the lack of selective auditory apperceptive disorders within neurological populations, and suggest that the cognitive independence of auditory apperception is limited; instead apperceptive processes may depend upon a distributed temporo-parietal network. At the same time however, rare accounts of relatively selective apperceptive deficits (Fujii et al., 1990; Habib et al., 1995; Griffiths et al., 1997; Wang et al., 2000; Saygin et al., 2010; Chapters 3 and 6) suggest that certain aspects of auditory apperception exhibit a degree of cognitive independence, which may arise from the relative functional specialisation of particular sub-regions of this non-verbal auditory processing network.

Further neuropsychological and neuroimaging research is required to characterise the relations between auditory apperception and other non-verbal auditory processes more fully. However, findings to date may suggest that mechanisms of object apperception in the auditory modality differ significantly from those previously described in the visual modality, in which cognitive and anatomical evidence more clearly points to an independent stage of processing (e.g., Warrington and Taylor, 1973; Warrington and James, 1988). Whilst it is difficult to provide direct support for this divergence, it might be suggested that humans have evolved modality-specific apperception mechanisms in response to modality-specific problems of everyday object processing. Specifically, whilst the key apperceptive problem in vision is likely to comprise recognising objects from unusual viewpoints (i.e., object invariance), the key apperceptive problem in audition might be segregating objects from complex backgrounds (i.e., auditory scene analysis, ASA). Although perception in both modalities also relies upon abilities for solving the less relevant problem (i.e., visual scene analysis, degraded sound recognition), apperceptive mechanisms might exhibit fundamental modality-specific biases. These conclusions therefore highlight the

pitfalls of uncritically transposing cognitive models between modalities, and emphasise the need to develop the concept of apperceptive processing via experimentation in a range of modalities.

7.2.4 Auditory semantic processing

The evidence of this thesis, considered alongside previous studies, suggests that auditory object recognition is not a unitary or independent stage of processing, and is better conceptualised as a range of interdependent perceptual and semantic cognitive functions. As outlined in the introduction, the collection of functions involved is likely to include mechanisms for perceptual representation, multi-modal semantic representation (involving information coded directly within one or more relevant modalities), and amodal semantic representation (involving information coded in abstract form, typically as patterns of statistical correlations between object features; see section 1.5.5.1). The various lines of evidence which support these assertions, taken from this thesis and elsewhere, will now be outlined.

Firstly, little evidence for selective auditory semantic deficits was derived from the current behavioural investigations (although stronger evidence might be found in studies of other neurological conditions such as herpes simplex virus encephalitis or stroke, which have previously been associated with modality- and category-specific semantic impairments). For example, parallel impairments in tests of visual and auditory semantic processing and auditory apperception were found in patients with SD (Chapter 2). Whilst results do not enable determination of the underlying cognitive basis of these impairments, previous research in SD strongly indicates a core disorder of amodal semantic representation (Hodges and Patterson, 1996; Bozeat et al., 2000; Mayberry et al,. 2010). Notably, this theoretical position would account for the current observation of simultaneous visual and auditory semantic deficits. Additionally, it would suggest that the observation of auditory apperceptive impairments indicates that corresponding brain processes normally rely upon top-down input from amodal semantic representations. Thus, the results of Chapter 2 indicate semantic mechanisms that are shared between modalities, and that are closely connected to apperceptive processes within the auditory modality.

Secondly, semantic deficits in PNFA, LPA and AD (Chapters 2, 3 and 4) were observed only alongside more severe deficits of perceptual (property and/or apperceptive) processing. Whilst it is once more difficult to judge whether data reflect multiple independent deficits, or a single primary disorder that gives rise to multiple deficits, it has already been argued that impairments for simple perceptual analysis are likely to lead to secondary impairments at more complex processing stages (e.g., section 7.1.1). Thus, it can be suggested that these data are unlikely to reflect damage to an independent stage of auditory semantic processing and instead may reflect close associations between auditory semantic and perceptual mechanisms.

Within this thesis, the clearest evidence that auditory object recognition depends upon a range of interdependent perceptual and semantic cognitive functions was provided by a functional imaging study of environmental sound listening in a group of SD patients (Chapter 5). Here, disease-related activity during both perceptual and semantic conditions traversed widespread temporal regions and extended into the inferior parietal lobe. Comparing this distribution of activity with previous work suggests not only an amodal semantic processing disorder, but also the involvement of perceptual (Wessinger et al., 2001) and multi-modal semantic (Lewis et al., 2005; Lewis et al., 2006; Pobric et al., 2010a) mechanisms. Further, overlapping patterns of disease-related activity during perceptual and semantic conditions indicate a close coupling between these different stages of processing. Such findings, together with previous evidence that SD involves damage to a distributed but functionally coherent cortical network (Seeley et al., 2009), suggest that perceptual and semantic stages of auditory object analysis are performed within a unified neural network traversing temporo-parietal brain regions. Further, given the primacy of semantic impairments in behavioural investigations of SD (e.g., Bozeat et al., 2000), it may be suggested that observed perceptual impairments reflect the top-down effects of disrupted semantic processes within such a network; however, further work is required to substantiate this claim.

This functional imaging investigation of auditory object listening in SD also provides insight into the causal anatomical substrates and cognitive processes involved in category-specific semantic sound analysis. Within the relevant

experimental contrast, the SD group showed disease-related activity throughout temporal and parietal regions, and additionally failed to activate the dorsal cortical pathway for processing tool sounds. Thus, findings provide important neuropsychological evidence for the dissociation of ventral and dorsal category-specific auditory object processing pathways previously described in healthy controls (e.g., Lewis et al., 2005; Lewis et al., 2006). Additionally, results implicate distributed temporo-parietal brain regions, previously associated with both auditory perceptual and semantic mechanisms, in the categorization of auditory objects; moreover, in the context of SD such findings are likely to signal the disruption of network-level brain mechanisms (Seeley et al., 2009). From this perspective, disease-related activity during category-specific processing might indicate a disruption of links between auditory perceptual and corresponding semantic representations that normally support mechanisms for differentiating sound categories prior to subsequent semantic analysis. In summary, findings suggest that the categorization of auditory objects depends upon a distributed temporo-parietal network involving interdependent mechanisms of perceptual and semantic processing; additionally, ventral and dorsal portions of this network may show relative functional specialization for the processing of particular sound categories.

Interdependencies between perceptual and semantic stages of non-verbal auditory object processing are supported by previous studies (e.g., Griffiths and Warren, 2004). For example, electrophysiological investigations showing reciprocal neural connections within animal auditory cortices provide an anatomical basis for such interdependences (Hackett et al., 1998; Eliades and Wang, 2008; Lee and Winer, 2008; Tourville et al., 2008). Additionally, one neuropsychological group study found that all subjects with an auditory semantic deficit had additional deficits in at least one perceptual task (Clarke et al., 1996). Finally, the neuroimaging of healthy controls during auditory object listening tasks regularly implicates distributed regions associated with perceptual, multi-modal semantic and amodal semantic mechanisms (Lewis et al., 2005; Lewis et al., 2006; Engel et al., 2009; Lewis et al., 2010), and furthermore, suggests that patterns of activity generated in perceptual and semantic conditions are substantially overlapping (e.g., Engel et al., 2009; Staeren et al., 2009; Lewis et al., 2010; Leaver and Rauschecker, 2010).

Notably, the current neuropsychological data augments these findings by suggesting that the different sub-processes highlighted, and their interdependencies, are not merely associated but causally related.

Together, current and previous evidence suggests that auditory object recognition is likely to occur via the concerted action of perceptual, multi-modal semantic and amodal semantic representations within a widespread temporo-parietal neural network. However, the previous literature also contains descriptions of category-specific auditory associative agnosia (Spreen et al., 1965; Eustache et al., 1990; Peretz, 1996; Garrido et al., 2009; Hailstone et al., 2010) and sub-regions that show preferential responses to particular sound categories (Belin et al., 2000; Scott et al., 2000; Belin et al., 2002; Belin and Zatorre, 2003; Zatorre et al., 2004; Warren et al., 2006; Leaver and Rauschecker, 2010). Therefore, the brain network for auditory semantic processing, whilst distributed, may contain regions of functional specialisation which support relatively independent category-specific mechanisms.

7.2.5 Mechanisms underlying the architecture of non-verbal auditory cognition

The evidence described above strongly suggests that non-verbal auditory cognition can be divided into multiple relatively independent sub-processes which nonetheless show interdependencies with one another. Further, such data indicate the action of distributed neural networks showing varying degrees of functional specialisation. Although this model of auditory processing is preliminary and awaits further evidence, analogous cognitive architectures have been proposed in the visual modality. For example, the functional imaging of visual object processing suggests that particular object categories are represented within certain circumscribed cortical regions (e.g., faces, places, buildings, body parts), whilst others are reliant upon the concerted activation of distributed regions (e.g., cars, scissors, chairs; Grill-Spector, 2003). Additionally, the examination of responses to object-relevant visual properties (e.g., shape, eccentricity) commonly reveals patterns of systematic topographical cortical organization. Specifically, visual properties appear to be represented within ‘maps’, in which incremental progression along the cortical

sheet elicits selective responses to continuously increasing (or decreasing) property levels (Grill-Spector, 2003; Op de Beeck et al., 2008). On the basis of this evidence, it has been suggested that the superimposition of multiple property maps may lead to the specialization of circumscribed cortical regions for particular object categories, by virtue of the particular combination of property values coded (Op de Beeck et al., 2008). For example, face selective regions might emerge from the coincidence of map-based preferences for curved lines, compact shapes, and foveal stimulation. In contrast, object categories that elicit distributed rather than regionally circumscribed activity might depend upon property combinations that are not topographically coincident. To summarize, work in visual cognition suggests that multiple superimposed property maps give rise to cortical regions with varying degrees of functional specialization; crucially, such topographical organisation provides an account of cognitive processes within a functionally coherent network that show varying degrees of independence.

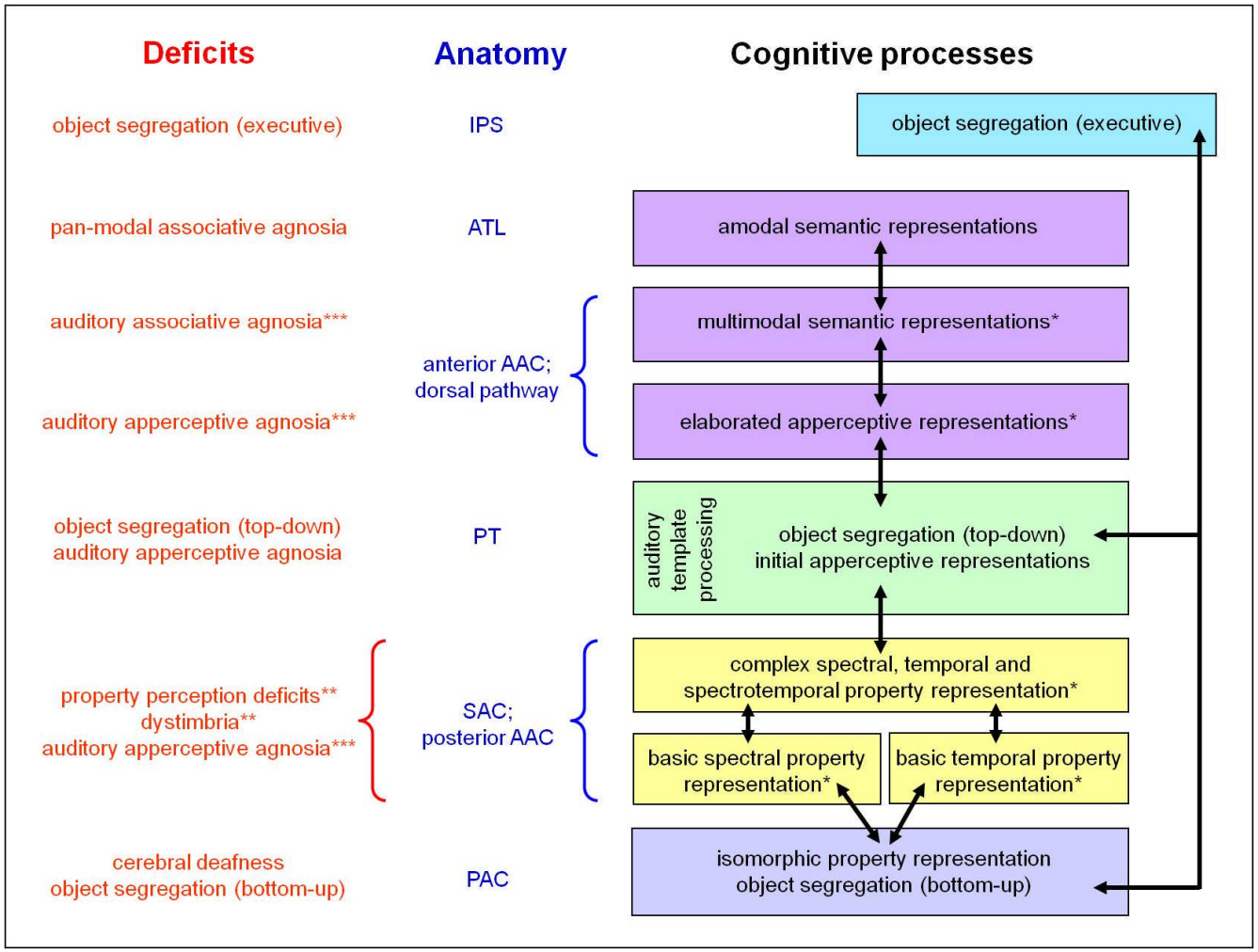
Although brain processes in distinct modalities are likely to show important functional differences, auditory object cognition may rely upon mechanisms that are similar to those described in the visual literature. For example, a range of evidence collected in animal and human populations indicates that primary and nearby non-primary auditory cortices contain topographical maps of a number of auditory properties including frequency (Bendor and Wang, 2008; Kaas and Hackett, 2000; Kosaki et al., 1997; Kusmierek and Rauschecker, 2009; Petkov et al., 2006; Rauschecker et al., 1995; Rauschecker and Tian, 2004), amplitude (Phillips et al, 1994; Bilecen, 2002), spectral bandwidth (Schreiner and Mendelson, 1990; Recanzone et al., 1999; Schreiner et al., 2000), and frequency modulation (Mendelson et al., 1993; Zhang et al., 2003). Whilst little topographic functional organisation has been reported beyond the primary auditory cortex, this may reflect the presence of highly complex, multidimensional and non-linear maps which so far remain undetected (Schreiner and Winer, 2007; Read et al., 2002). It is therefore plausible that the superimposition of multiple auditory property maps might account for both circumscribed (Belin et al., 2000; Scott et al., 2000; Belin et al., 2002; Belin and Zatorre, 2003; Zatorre et al, 2004; Warren et al., 2006; Leaver and Rauschecker, 2010) and distributed (Staeren et al., 2009; Leaver and

Rauschecker, 2010) cortical representations of particular sound categories. Further, at least one study has provided direct empirical evidence for this hypothesis: in healthy human subjects, Lewis and colleagues (2009) demonstrated the anatomical proximity of regions that are selectively responsive to a particular category of sound (human vocalisations), and those that show parametric responses to category-relevant perceptual properties (spectral complexity). Taken together, whilst a great deal of work is required to test these ideas in the auditory modality, a functional architecture based upon the superimposition of multiple property maps would account for the observations here, and elsewhere, that sub-processes of non-verbal auditory processing show degrees of both independence and interdependence.

7.2.6 Towards a model of non-verbal auditory cognition

Based on the evidence reviewed above, a preliminary cognitive model of non-verbal auditory processing can be proposed (Figure 7.1, page 295). It must be emphasized, however, that the model and its anatomical attributions are tentative, since the body of data on which they are based is relatively slight. The model is intended to depict a distributed processing network in which boxes represent sub-processes showing relative rather than absolute levels of cognitive independence and anatomical specialisation. It is likely that many of the constituent boxes subdivide into multiple relatively independent property- or category-specific processes; however, insufficient evidence is available to depict these subdivisions in the current model. Important interdependencies between sub-processes are indicated by arrows: uni- and bi-directional arrows signify bottom-up and reciprocal connections respectively. Finally, whilst the effects of general cognitive processes such as attention and working memory are not shown, these are presumed to affect all stages of the model.

Figure 7.1 A preliminary cognitive model of non-verbal auditory object processing



Complex and basic stages of property representation refer to perceptual mechanisms that are more or less likely to provide key inputs to the analysis of whole object representations. KEY: *, processing stage likely to show cognitive/anatomical specialisation for certain auditory properties and/or sound categories; **, deficits may affect the processing of restricted auditory properties; ***, deficits may affect the processing of restricted auditory categories; ATL, anterior temporal lobe; IPS, intra-parietal sulcus; PT, planum temporale; AAC, auditory association cortices; SAC, secondary auditory cortex; PAC primary auditory cortex.

7.2.7 Directions for future work

The findings of this thesis are preliminary and will require corroboration and development in future studies. Thus, some suggestions for the particular directions that further work might take will now be outlined.

Firstly, results derived from the group investigations of this thesis require validation in studies involving larger cohorts, additional neurological patient groups, longitudinal paradigms, and independent cognitive measures. Here, group investigations took the form of cross-sectional studies involving small subject numbers (in part due to the rarity of syndromes under investigation), and preliminary cognitive tests that may have failed to map onto core processes of non-verbal auditory cognition. Thus, large scale (and possibly multi-site) longitudinal investigations using independent cognitive measures would increase experimental power, the reliability of findings, and ultimately, the scientific understanding of non-verbal auditory processing. Further such studies would also provide the opportunity to develop standardised non-verbal auditory cognitive measures; in turn, the availability of such measures in the future would increase the quantity and comparability of large and small studies alike, thus facilitating further insight into mechanisms of non-verbal auditory processing. Finally, such work would enhance understanding of the cognitive signatures of various dementia syndromes, thus increasing the consequent clinical and research benefits described above (sections 7.1.5 and 7.1.6).

Secondly, neuroimaging studies of patients are required to reveal the anatomical correlates of non-verbal auditory disorders, and by inference, the neural architecture of corresponding cognitive processes. Whilst there already exists a burgeoning literature of relevant functional imaging studies in healthy subjects, analogous investigations involving neurological patients will facilitate the differentiation of essential from auxiliary substrates. Further, imaging studies of dementia subjects, who suffer cortical degeneration to functionally coherent regions, are likely to reveal the network-level characteristics of non-verbal auditory processing. In particular, strong evidence is likely to be provided by either combined spatial and temporal imaging techniques (e.g., simultaneous fMRI and MEG), or the use of methods that enable the visualisation of structural

and functional connectivity patterns (e.g., diffusion tensor imaging, dynamic causal modelling, multivariate pattern analysis). Such investigations would be particularly well placed to answer some of the most pressing questions emerging from this body of work. For example, whilst current findings indicate that none of the broad stages of non-verbal auditory cognition are unitary, they do not establish the details of implicated sub-processes; relevant neuroimaging studies might reveal the anatomical, and by inference, cognitive loci of such sub-processes. Additionally, whilst this thesis highlighted the potential importance of interdependencies between various stages of non-verbal auditory (and non-auditory) cognition, future imaging studies might reveal the relative strengths and directions of such links. Together, such studies would therefore provide considerable insight into sub-processes of non-verbal auditory processing, and their interrelationships within distributed neural networks.

8 Appendices

8.1 Glossary

agnosia	A general term referring to any deficit of object processing; cf. apperceptive agnosia, associative agnosia.
apperceptive processing	The perceptual processing of whole object representations.
apperceptive agnosia	A selective deficit in the perceptual processing of whole object representations; cf. associative agnosia.
apperceptive phonagnosia	A deficit in the perceptual processing of voices, manifest as an inability to discriminate between different voices.
associative agnosia	A selective deficit in the semantic processing of whole object representations; cf. apperceptive agnosia.
associative phonagnosia	A selective deficit in the semantic processing of voices, manifest as an inability to recognise individuals by their voices.
auditory agnosia	A general term referring to any deficit of object processing in the auditory modality.
auditory association cortex	A relatively large region of the superior temporal lobes involved in auditory processing, including anterior and posterior regions of the superior temporal sulcus and gyrus. Auditory association cortex is typically associated with the representation of complex auditory percepts.
auditory object	Any collection of auditory perceptual properties bound in a single perceptual representation and disambiguated from the auditory scene.
auditory scene analysis (ASA)	The process by which the auditory scene is parsed into constituent sound objects.
auditory template	Structural or perceptual (i.e., spectrotemporal) representations of auditory objects, which may code complex non-linear associations between spectral and temporal properties to emphasise object-relevant (rather than basic physical) information. Auditory templates may provide a cognitive substrate for auditory object apperception, to facilitate both the discrimination of objects under changing listening conditions (i.e., auditory object invariance) and auditory scene analysis.
bottom-up processing	In auditory scene analysis, processes that involve the organisation of the auditory scene according to simple acoustic properties, i.e. properties typically coded in the form of direct isomorphic representations.
complex sound	A sound carrying energy at more than one frequency simultaneously.
dystimbria	A deficit of timbre processing.
fMRI	functional magnetic resonance imaging
fundamental frequency	The fundamental frequency gives the pitch of a complex sound, and is equal to the highest frequency for which each harmonic is an integer multiple, or the frequency spacing between consecutive harmonics.

harmonic structure	A particular form of spectral shape featuring energy at multiple, regularly spaced frequency values, known as harmonics; harmonic structures are typical of human and animal vocalisations, and musical instruments.
isomorphic	Isomorphic representations directly code the physical structure of stimuli, without emphasising any particular properties; cf. perceptual.
missing fundamental pitch	A phenomenon in which the fundamental frequency of a complex sound gives the pitch, even when there is no energy present at the fundamental frequency.
noise	Auditory noise contains relatively equal amounts of energy across a wide range of frequencies, and therefore tends to lack harmonic structure and pitch; noisy sounds are typically made by weather, machinery, tools and engines.
object invariance	The consistent recognition of an object despite varying perceptual information. For example, in the visual modality, objects can be recognised from varying perspectives, and in the auditory modality, objects can be recognised despite varying levels of background noise.
object processing	The processing of object representations, i.e. collections of perceptual properties bound in unified representations to represent a singular entity in the world.
perceptual	Perceptual representations do not directly code the physical structure of stimuli, but instead emphasise and de-emphasise important and unimportant aspects of stimuli respectively. Perceptual representations are therefore held to contain complex non-linear mappings of physical stimulus structure; cf. isomorphic.
perceptual property processing	Perceptual processing of any auditory property that does not constitute a whole auditory object, for example, in the auditory modality, the processing of pitch or timbre; cf. apperceptive processing.
peripheral deafness	A complete or partial inability to detect and/or perceive all sound, following damage to the peripheral auditory system (at the ear or the cochlea). Mild peripheral deafness, affecting the ability to hear high frequencies, is common in older adult populations.
phonagnosia	A general term referring to deficits for the processing of voices; cf. perceptual phonagnosia, associative phonagnosia.
pitch	The perceptual property that allows sounds to be ordered on a musical scale from ‘low’ to ‘high’. Pitch is a percept, defined psychoacoustically rather than physically, since the same pitch can be evoked by a range of physically different stimuli.
primary auditory cortex (PAC)	The first cortical region involved in auditory processing, physically located midway along the superior temporal plane in medial Heschl’s gyrus. PAC preferentially encodes the simplest sound properties.
pure tone	The simplest type of sound wave, consisting of energy at a single frequency.
secondary auditory cortex	Secondary auditory cortex is a direct recipient of information from primary auditory cortex, and is situated in lateral Heschl's gyrus in the superior temporal plane. Secondary auditory cortex preferentially encodes relatively simple perceptual auditory properties such as pitch.

semantic (associative) processing	The association of stored knowledge, or semantic memory, with perceptual object representations.
spectral	In any sound, a general term referring to the distribution of energy across different frequencies; cf. spectral shape, spectral modulation.
spectral modulation	In any sound, fluctuations of energy across the frequency range; these may occur at different rates (resolutions), i.e., across narrow to broad frequency ranges.
spectral shape	In any sound, the detailed profile of energy levels across the full range of frequencies (without differentiation between time points); in plots of spectral shape, the x axis represents frequency and the y axis represents energy level.
spectrogram	A conjoint graphical representation of temporal and spectral shape; time and frequency are represented along the x and y axes respectively, and the energy level at any time-frequency combination is indicated by the colour of the corresponding point in the plot, on a scale varying from high (hot colours) to low (cool colours).
spectrotemporal	In any sound, the information provided by the conjunction of spectral and temporal structure (as opposed to the information provided by spectral and temporal structures individually).
spectrotemporal signature	A stereotypical spectrotemporal profile that is typically associated with a particular sound or sound category.
temporal	In any sound, a general term referring to the distribution of energy across time; cf. temporal shape, temporal modulation.
temporal modulation	In any sound, fluctuations of energy across time; these may occur at different rates (resolutions), i.e., from fast to slow.
temporal shape	In any sound, the detailed profile of energy levels across different time points (without differentiation between frequencies); in plots of temporal shape, the x axis represents time and the y axis represents energy level.
timbre	The perceptual property that distinguishes two sounds of identical pitch, loudness and duration; perceptually, it might be equated loosely with sound ‘quality’ or ‘colour’. Timbre is a multi-dimensional property, influenced by spectral, temporal, and spectrotemporal structure, and therefore cannot be ordered along a single perceptual scale.
top-down processing	In auditory scene analysis, processes that involve the organisation of acoustic components according to prior knowledge, i.e., those typically coded in the form of auditory templates.
word deafness	A selective deficit for the perception or recognition of spoken words, or speech. Several subtypes of word deafness exist, involving distinct underlying cognitive deficits. However, the syndrome most commonly involves an auditory perceptual property processing impairment that particularly affects words, by virtue of their typical acoustic structure.

8.2 Abbreviations

AD	Alzheimer's disease (typical variant)
AM	amplitude modulation
ASA	auditory scene analysis
ATL	anterior temporal lobe
BOLD	blood-oxygen-level-dependent
CI	confidence interval
DTI	diffusion tensor imaging
EEG	electroencephalography
EPI	echoplanar image
ERP	event-related potential
FM	frequency modulation
fMRI	functional magnetic resonance imaging
FTLD	fronto-temporal lobar degeneration
FWE	family-wise error
GAA	progranulin associated aphasia
GRN	progranulin gene
HG	Heschl's gyrus
IFL	inferior frontal lobe
IPL	inferior parietal lobe
IPS	intra-parietal sulcus
ISI	inter-stimulus interval
ITG	inferior temporal gyrus
LPA	logopenic (phonological) aphasia
MEG	magnetoencephalography
MMSE	mini-mental state examination (Folstein et al., 1975)
MRI	magnetic resonance image
MTG	middle temporal gyrus
PAC	primary auditory cortex
PFC	pre-frontal cortex
pLaS	posterior lateral sulcus
PNFA	progressive non-fluent aphasia
PP	planum polare
PPA	primary progressive aphasia
PT	planum temporale
PTA	pure tone audiometry
RT	reaction time
rTMS	repetitive trans-cranial magnetic stimulation
SD	semantic dementia
STG/STP/STS	superior temporal gyrus/plane/sulcus
TPJ	temporo-parietal junction
VBM	voxel-based morphometry
VDM	voxel displacement map

8.3 References

Adduri, C.A., Marotta, J.J., 2009. Mental rotation of faces in healthy aging and Alzheimer's disease. PLoS One. 4, e6120.

Agosta, F., Henry, R.G., Migliaccio, R., Neuhaus, J., Miller, B.L., Dronkers, N.F., Brambati, S.M., Filippi, M., Ogar, J.M., Wilson, S.M., Gorno-Tempini, M.L., 2010. Language networks in semantic dementia. Brain. 133, 286-299.

Alain, C., He, Y., Grady, C., 2008. The contribution of the inferior parietal lobe to auditory spatial working memory. J Cogn Neurosci. 20, 285-295.

Alain, C., Arnott, S.R., 2000. Selectively attending to auditory objects. Front Biosci. 5, D202-12.

Albert, M.L., Bear, D., 1974. Time to understand. A case study of word deafness with reference to the role of time in auditory comprehension. Brain. 97, 373-384.

Altmann, C.F., Junior, C.G., Heinemann, L., Kaiser, J., 2010. Processing of spectral and amplitude envelope of animal vocalizations in the human auditory cortex. Neuropsychologia. 48, 2824-2832.

Anaki, D., Kaufman, Y., Freedman, M., Moscovitch, M., 2007. Associative (prosop)agnosia without (apparent) perceptual deficits: a case-study. Neuropsychologia. 45, 1658-1671.

Ash, S., McMillan, C., Gunawardena, D., Avants, B., Morgan, B., Khan, A., Moore, P., Gee, J., Grossman, M., 2010. Speech errors in progressive non-fluent aphasia. Brain Lang. 113, 13-20.

Auerbach, S.H., Allard, T., Naeser, M., Alexander, M.P., Albert, M.L., 1982. Pure word deafness. Analysis of a case with bilateral lesions and a defect at the prephonemic level. Brain. 105, 271-300.

Ayotte, J., Peretz, I., Rousseau, I., Bard, C., Bojanowski, M., 2000. Patterns of music agnosia associated with middle cerebral artery infarcts. Brain. 123 (Pt 9), 1926-1938.

Baddeley, A., 2000. The episodic buffer: a new component of working memory? Trends Cogn Sci. 4, 417-423.

Baird, A., Samson, S., 2009. Memory for music in Alzheimer's disease: unforgettable? Neuropsychol Rev. 19, 85-101.

Baldo, J.V., Dronkers, N.F., 2006. The role of inferior parietal and inferior frontal cortex in working memory. Neuropsychology. 20, 529-538.

Baloyannis, S.J., 2009. Dendritic pathology in Alzheimer's disease. J Neurol Sci. 283, 153-157.

Bar-Yosef, O., Nelken, I., 2007. The effects of background noise on the neural responses to natural sounds in cat primary auditory cortex. Front Comput Neurosci. 1, 3.

Barrett, D.J., Edmondson-Jones, A.M., Hall, D.A., 2009. Attention in neglect and extinction: Assessing the degree of correspondence between visual and auditory impairments using matched tasks. J Clin Exp Neuropsychol., 1-12.

Barsalou, L.W., Kyle, S.W., Barbey, A.K., Wilson, C.D., 2003. Grounding conceptual knowledge in modality-specific systems. Trends Cogn Sci. 7, 84-91.

Belin, P., Zatorre, R.J., 2003. Adaptation to speaker's voice in right anterior temporal lobe. Neuroreport. 14, 2105-2109.

Belin, P., Zatorre, R.J., Ahad, P., 2002. Human temporal-lobe response to vocal sounds. Brain Res Cogn Brain Res. 13, 17-26.

Belin, P., Zatorre, R.J., Lafaille, P., Ahad, P., Pike, B., 2000. Voice-selective areas in human auditory cortex. Nature. 403, 309-312.

Bendor, D., Wang, X., 2008. Neural response properties of primary, rostral, and rostrotemporal core fields in the auditory cortex of marmoset monkeys. J Neurophysiol. 100, 888-906.

Bendor, D., Wang, X., 2005. The neuronal representation of pitch in primate auditory cortex. Nature. 436, 1161-1165.

Bilecen, D., Seifritz, E., Scheffler, K., Henning, J., Schulte, A.C., 2002. Amplitopicity of the human auditory cortex: an fMRI study. Neuroimage. 17, 710-718.

Binder, J.R., Desai, R.H., Graves, W.W., Conant, L.L., 2009. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex. 19, 2767-2796.

Binder, J.R., Frost, J.A., Hammeke, T.A., Bellgowan, P.S., Springer, J.A., Kaufman, J.N., Possing, E.T., 2000. Human temporal lobe activation by speech and nonspeech sounds. Cereb Cortex. 10, 512-528.

Bishop, D.V., 1989. Test for reception of grammar. MRC Applied Psychology Unit, Cambridge, UK.

Boemio, A., Fromm, S., Braun, A., Poeppel, D., 2005. Hierarchical and asymmetric temporal sensitivity in human auditory cortices. Nat Neurosci. 8, 389-395.

Bonner, M.F., Ash, S., Grossman, M., 2010. The new classification of primary progressive aphasia into semantic, logopenic, or nonfluent/agrammatic variants. Curr Neurol Neurosci Rep. 10, 484-490.

Boumans, T., Theunissen, F.E., Poirier, C., Van Der Linden, A., 2007. Neural representation of spectral and temporal features of song in the auditory forebrain of zebra finches as revealed by functional MRI. Eur J Neurosci. 26, 2613-2626.

Bozeat, S., Lambon Ralph, M.A., Graham, K.S., Patterson, K., Wilkin, H., Rowland, J., Rogers, T.T., Hodges, J.R., 2003. A duck with four legs: Investigating the structure of conceptual knowledge using picture drawing in semantic dementia. Cogn Neuropsychol. 20, 27-47.

Bozeat, S., Lambon Ralph, M.A., Patterson, K., Hodges, J.R., 2002. When objects lose their meaning: what happens to their use? Cogn Affect Behav Neurosci. 2, 236-251.

Bozeat, S., Lambon Ralph, M.A., Patterson, K., Garrard, P., Hodges, J.R., 2000. Non-verbal semantic impairment in semantic dementia. Neuropsychologia. 38, 1207-1215.

Bregman, A.S., 1990. Auditory scene analysis : the perceptual organization of sound. MIT Press, Cambridge, Mass.

Bright, P., Moss, H.E., Stamatakis, E.A., Tyler, L.K., 2008. Longitudinal studies of semantic dementia: the relationship between structural and functional changes over time. Neuropsychologia. 46, 2177-2188.

Buchtel, H.A., Stewart, J.D., 1989. Auditory agnosia: apperceptive or associative disorder? Brain Lang. 37, 12-25.

Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R.A., Johnson, K.A., 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J Neurosci. 29, 1860-1873.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann NY Acad Sci. 1124:1-38., 1-38.

Buckner, R.L., Snyder, A.Z., Shannon, B.J., LaRossa, G., Sachs, R., Fotenos, A.F., Sheline, Y.I., Klunk, W.E., Mathis, C.A., Morris, J.C., Mintun, M.A., 2005. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci. 25, 7709-7717.

Bussey, T.J., Saksida, L.M., 2002. The organization of visual object representations: a connectionist model of effects of lesions in perirhinal cortex. Eur J Neurosci. 15, 355-364.

Caine, D., Breen, N., Patterson, K., 2009. Emergence and progression of 'non-semantic' deficits in semantic dementia. Cortex. 45, 483-494.

Caramazza, A., Shelton, J.R., 1998. Domain-specific knowledge systems in the brain the animate-inanimate distinction. J Cogn Neurosci. 10, 1-34.

Caramazza, A., Berndt, R.S., Basili, A.G., 1983. The selective impairment of phonological processing: a case study. Brain Lang. 18, 128-174.

Carlesimo, G.A., Casadio, P., Sabbadini, M., Caltagirone, C., 1998. Associative visual agnosia resulting from a disconnection between intact visual memory and semantic systems. Cortex. 34, 563-576.

Carlyon, R.P., Plack, C.J., Fantini, D.A., Cusack, R., 2003. Cross-modal and non-sensory influences on auditory streaming. Perception. 32, 1393-1402.

Carlyon, R.P., Cusack, R., Foxton, J.M., Robertson, I.H., 2001. Effects of attention and unilateral neglect on auditory stream segregation. J Exp Psychol Hum Percept Perform. 27, 115-127.

Chertkow, H., Whatmough, C., Saumier, D., Duong, A., 2008. Cognitive neuroscience studies of semantic memory in Alzheimer's disease. Prog Brain Res. 169:393-407., 393-407.

Chertkow, H., Bub, D., 1990. Semantic memory loss in dementia of Alzheimer's type. What do various measures measure? Brain. 113, 397-417.

Chi, T., Ru, P., Shamma, S.A., 2005. Multiresolution spectrotemporal analysis of complex sounds. J Acoust Soc Am. 118, 887-906.

Chi, T., Gao, Y., Guyton, M.C., Ru, P., Shamma, S., 1999. Spectro-temporal modulation transfer functions and speech intelligibility. J Acoust Soc Am. 106, 2719-2732.

Chomsky, N., 1980. Rules and representations. Behav Brain Sci, 1-61.

Clarke, S., Bellmann, A., De Ribaupierre, F., Assal, G., 1996. Non-verbal auditory recognition in normal subjects and brain-damaged patients: evidence for parallel processing. Neuropsychologia. 34, 587-603.

Coccia, M., Bartolini, M., Luzzi, S., Provinciali, L., Lambon Ralph, M.A., 2004. Semantic memory is an amodal, dynamic system: Evidence from the interaction of naming and object use in semantic dementia. Cogn Neuropsychol. 21, 513-527.

Coen, R.F., Kirby, M., Swanwick, G.R., Maguire, C.P., Walsh, J.B., Coakley, D., O'Neill, D., Lawlor, B.A., 1997. Distinguishing between patients with depression or very mild Alzheimer's disease using the Delayed-Word-Recall test. Dement Geriatr Cogn Disord. 8, 244-247.

Coltheart, M., 1985. Cognitive neuropsychology and the study of reading. Attention and performance XI. Erlbaum, Hillsdale, NJ, pp. 3-37.

Confavreux, C., Croisile, B., Garassus, P., Aimard, G., Trillet, M., 1992. Progressive amusia and aprosody. Arch Neurol. 49, 971-976.

Crawford, J.R., Garthwaite, P.H., 2002. Investigation of the single case in neuropsychology: confidence limits on the abnormality of test scores and test score differences. Neuropsychologia. 40, 1196-1208.

Crawford, J.R., Garthwaite, P.H., 2005. Testing for suspected impairments and dissociations in single-case studies in neuropsychology: evaluation of alternatives using monte carlo simulations and revised tests for dissociations. Neuropsychology. 19, 318-331.

Croot, K., Patterson, K., Hodges, J.R., 1998. Single word production in nonfluent progressive aphasia. Brain Lang. 61, 226-273.

Crutch, S.J., Warrington, E.K., submitted. Different patterns of spoken and written word comprehension deficit in stroke patients.

Crutch, S.J., Warrington, E.K., 2003. The selective impairment of fruit and vegetable knowledge: a multiple processing channels account of fine-grained category specificity. Cognitive Neuropsychology. 20, 355-372.

Cusack, R., 2005. The intraparietal sulcus and perceptual organization. J Cogn Neurosci. 17, 641-651.

Cusack, R., Deeks, J., Aikman, G., Carlyon, R.P., 2004. Effects of location, frequency region, and time course of selective attention on auditory scene analysis. J Exp Psychol Hum Percept Perform. 30, 643-656.

Cusack, R., Carlyon, R.P., Robertson, I.H., 2000. Neglect between but not within auditory objects. J Cogn Neurosci. 12, 1056-1065.

Cuzick, J., 1985. A Wilcoxon-type test for trend. Stat Med. 4, 87-90.

Damasio, A.R., 1989. The brain binds entities and events by multiregional activation from convergence zones. Neural Computation. 1, 123-132.

Davis, A., MRC Institute of Hearing Research., 1995. Hearing in adults : the prevalence and distribution of hearing impairment and reported hearing disability in the MRC Institute of Hearing Research's National Study of Hearing. Whurr Publishers, London.

De Renzi, E., Lucchelli, F., 1994. Are semantic systems separately represented in the brain? The case of living category impairment. Cortex. 30, 3-25.

De Renzi, E., Scotti, G., Spinnler, H., 1969. Perceptual and associative disorders of visual recognition. Relationship to the side of the cerebral lesion. Neurology. 19, 634-642.

Deichmann, R., Schwarzbauer, C., Turner, R., 2004. Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3 T. Neuroimage. 21, 757-767.

Deike, S., Scheich, H., Brechmann, A., 2010. Active stream segregation specifically involves the left human auditory cortex. Hear Res. 265, 30-37.

Deike, S., Gaschler-Markefski, B., Brechmann, A., Scheich, H., 2004. Auditory stream segregation relying on timbre involves left auditory cortex. Neuroreport. 15, 1511-1514.

Dekosky, S.T., Lopez, O.L., 2007. Alzheimer's Disease. In: Growdon, J.H., Rossor, M.N. (Eds.), The Dementias 2. Butterworth-Heinemann, Philadelphia, pp. 33-58.

Delis, D.C., Kaplan, E., Kramer, J.H., 2001. Delis-Kaplan executive function system. The Psychological Corporation, San Antonio, Texas.

Demany, L., Carlyon, R.P., Semal, C., 2009. Continuous versus discrete frequency changes: different detection mechanisms? J Acoust Soc Am. 125, 1082-1090.

Depireux, D.A., Simon, J.Z., Klein, D.J., Shamma, S.A., 2001. Spectro-temporal response field characterization with dynamic ripples in ferret primary auditory cortex. J Neurophysiol. 85, 1220-1234.

Devlin, J.T., Gonnerman, L.M., Andersen, E.S., Seidenberg, M.S., 1998. Category-specific semantic deficits in focal and widespread brain damage: a computational account. J Cogn Neurosci. 10, 77-94.

Dooley, G.J., Moore, B.C., 1988. Duration discrimination of steady and gliding tones: a new method for estimating sensitivity to rate of change. J Acoust Soc Am. 84, 1332-1337.

Dubois, B., Feldman, H.H., Jacova, C., Dekosky, S.T., Barberger-Gateau, P., Cummings, J., Delacourte, A., Galasko, D., Gauthier, S., Jicha, G., Meguro, K., O'brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway, S., Stern, Y., Visser, P.J., Scheltens, P., 2007. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 6, 734-746.

Dunn, L.M., Whetton, C., Dunn, L.M., 1982. British picture vocabulary scale. NFER-Nelson, Windsor.

Ekman, P., Friesen, W.V., 1971. Constants across cultures in the face and emotion. J Pers Soc Psychol. 17, 124-129.

Eliades, S.J., Wang, X., 2008. Neural substrates of vocalization feedback monitoring in primate auditory cortex. Nature. 453, 1102-1106.

Elliott, T.M., Theunissen, F.E., 2009. The modulation transfer function for speech intelligibility. PLoS Comput Biol 5, e1000302.

Ellis, W.D., 1938. A sourcebook of Gestalt psychology. Routledge & Kegan Paul, London.

Engel, L.R., Frum, C., Puce, A., Walker, N.A., Lewis, J.W., 2009. Different categories of living and non-living sound-sources activate distinct cortical networks. Neuroimage. 47, 1778-1791.

Eustache, F., Lambert, J., Cassier, C., Dary, M., Rossa, Y., Rioux, P., Viader, F., Lechevalier, B., 1995. Disorders of auditory identification in dementia of the Alzheimer type. Cortex. 31, 119-127.

Eustache, F., Lechevalier, B., Viader, F., Lambert, J., 1990. Identification and discrimination disorders in auditory perception: a report on two cases. Neuropsychologia. 28, 257-270.

Feldman, J., 2003. What is a visual object? Trends Cogn Sci. 7, 252-256.

Fery, P., Morais, J., 2003. A Case Study of Visual Agnosia without Perceptual Processing or Structural Descriptions Impairment. Cogn Neuropsychol. 20, 595-618.

Fishman, Y.I., Steinschneider, M., 2010. Neural correlates of auditory scene analysis based on inharmonicity in monkey primary auditory cortex. J Neurosci. 30, 12480-12494.

Fishman, Y.I., Arezzo, J.C., Steinschneider, M., 2004. Auditory stream segregation in monkey auditory cortex: effects of frequency separation, presentation rate, and tone duration. J Acoust Soc Am.116, 1656-1670.

Fishman, Y.I., Reser, D.H., Arezzo, J.C., Steinschneider, M., 2001. Neural correlates of auditory stream segregation in primary auditory cortex of the awake monkey. Hear Res. 151, 167-187.

Fodor, J.A., 1983. The modularity of mind. MIT Press, Cambridge MA.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 12, 189-198.

Foxton, J.M., Dean, J.L., Gee, R., Peretz, I., Griffiths, T.D., 2004. Characterization of deficits in pitch perception underlying 'tone deafness'. Brain. 127, 801-810.

Franklin, S., Turner, J., Lambon Ralph, M.A., Morris, J., Bailey, P.J., 1996. A Distinctive Case of Word Meaning Deafness? Cognitive Neuropsychology. 13, 1139-1162.

Fujii, T., Fukatsu, R., Watabe, S., Ohnuma, A., Teramura, K., Kimura, I., Saso, S., Kogure, K., 1990. Auditory sound agnosia without aphasia following a right temporal lobe lesion. Cortex. 26, 263-268.

Fujimori, M., Imamura, T., Yamashita, H., Hirono, N., Mori, E., 1997. The disturbances of object vision and spatial vision in Alzheimer's disease. Dement Geriatr Cogn Disord. 8, 228-231.

Gainotti, G., 2004. A metanalysis of impaired and spared naming for different categories of knowledge in patients with a visuo-verbal disconnection. Neuropsychologia. 42, 299-319.

Gainotti, G., Barbier, A., Marra, C., 2003. Slowly progressive defect in recognition of familiar people in a patient with right anterior temporal atrophy. Brain. 126, 792-803.

Garrido, L., Eisner, F., McGettigan, C., Stewart, L., Sauter, D., Hanley, J.R., Schweinberger, S.R., Warren, J.D., Duchaine, B., 2009. Developmental phonagnosia: a selective deficit of vocal identity recognition. Neuropsychologia. 47, 123-131.

Gates, G.A., Anderson, M.L., Feeney, M.P., McCurry, S.M., Larson, E.B., 2008. Central auditory dysfunction in older persons with memory impairment or Alzheimer dementia. Arch Otolaryngol Head Neck Surg. 134, 771-777.

Gates, G.A., Beiser, A., Rees, T.S., D'Agostino, R.B., Wolf, P.A., 2002. Central auditory dysfunction may precede the onset of clinical dementia in people with probable Alzheimer's disease. J Am Geriatr Soc. 50, 482-488.

Gates, G.A., Cobb, J.L., Linn, R.T., Rees, T., Wolf, P.A., D'Agostino, R.B., 1996. Central auditory dysfunction, cognitive dysfunction, and dementia in older people. Arch Otolaryngol Head Neck Surg. 122, 161-167.

Giraud, A.L., Lorenzi, C., Ashburner, J., Wable, J., Johnsrude, I., Frackowiak, R., Kleinschmidt, A., 2000. Representation of the temporal envelope of sounds in the human brain. J Neurophysiol. 84, 1588-1598.

Glenberg, A.M., Kaschak, M.P., 2002. Grounding language in action. Psycho Bull Rev. 9, 558-565.

Golob, E.J., Ringman, J.M., Irimajiri, R., Bright, S., Schaffer, B., Medina, L.D., Starr, A., 2009. Cortical event-related potentials in preclinical familial Alzheimer disease. Neurology. 73, 1649-1655.

Golob, E.J., Irimajiri, R., Starr, A., 2007. Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. Brain. 130, 740-752.

Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M., 2011. Classification of primary progressive aphasia and its variants. Neurology. 76, 1006-14

Gorno-Tempini, M.L., Brambati, S.M., Ginex, V., Ogar, J., Dronkers, N.F., Marcone, A., Perani, D., Garibotto, V., Cappa, S.F., Miller, B.L., 2008. The logopenic/phonological variant of primary progressive aphasia. Neurology. 71, 1227-1234.

Gorno-Tempini, M.L., Dronkers, N.F., Rankin, K.P., Ogar, J.M., Phengrasamy, L., Rosen, H.J., Johnson, J.K., Weiner, M.W., Miller, B.L., 2004. Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol. 55, 335-346.

Greene, J.D., Hodges, J.R., 1996a. Identification of famous faces and famous names in early Alzheimer's disease. Relationship to anterograde episodic and general semantic memory. Brain. 119, 111-128.

Greene, J.D., Hodges, J.R., 1996b. The fractionation of remote memory. Evidence from a longitudinal study of dementia of Alzheimer type. Brain. 119, 129-142.

Griffiths, T.D., Kumar, S., Warren, J.D., Stewart, L., Stephan, K.E., Friston, K.J., 2007. Approaches to the cortical analysis of auditory objects. Hear Res. 229, 46-53.

Griffiths, T.D., Warren, J.D., 2004. What is an auditory object? Nat Rev Neurosci. 5, 887-892.

Griffiths, T.D., Warren, J.D., 2002. The planum temporale as a computational hub. Trends Neurosci. 25, 348-353.

Griffiths, T.D., Dean, J.L., Woods, W., Rees, A., Green, G.G., 2001. The Newcastle Auditory Battery (NAB). A temporal and spatial test battery for use on adult naive subjects. Hear Res. 154, 165-169.

Griffiths, T.D., Rees, A., Green, G.G.R., 1999. Disorders of human complex sound processing. Neurocase. 5, 365-378.

Griffiths, T.D., Buchel, C., Frackowiak, R.S., Patterson, R.D., 1998. Analysis of temporal structure in sound by the human brain. Nat Neurosci. 1, 422-427.

Griffiths, T.D., Rees, A., Witton, C., Cross, P.M., Shakir, R.A., Green, G.G., 1997. Spatial and temporal auditory processing deficits following right hemisphere infarction. A psychophysical study. Brain. 120 (Pt 5), 785-794.

Grill-Spector, K., 2003. The neural basis of object perception. Curr Opin Neurobiol. 13, 159-166.

Grossman, M., Koenig, P., Glosser, G., DeVita, C., Moore, P., Rhee, J., Detre, J., Alsop, D., Gee, J., 2003. Neural basis for semantic memory difficulty in Alzheimer's disease: an fMRI study. Brain. 126, 292-311.

Grossman, M., Rhee, J., Moore, P., 2005. Sentence processing in frontotemporal dementia. Cortex. 41, 764-777.

Gutschalk, A., Oxenham, A.J., Micheyl, C., Wilson, E.C., Melcher, J.R., 2007. Human cortical activity during streaming without spectral cues suggests a general neural substrate for auditory stream segregation. J Neurosci. 27, 13074-13081.

Gutschalk, A., Patterson, R.D., Scherg, M., Uppenkamp, S., Rupp, A., 2004. Temporal dynamics of pitch in human auditory cortex. Neuroimage. 22, 755-766.

Habib, M., Daquin, G., Milandre, L., Royere, M.L., Rey, M., Lanteri, A., Salamon, G., Khalil, R., 1995. Mutism and auditory agnosia due to bilateral insular damage--role of the insula in human communication. Neuropsychologia. 33, 327-339.

Hackett, T.A., Stepniewska, I., Kaas, J.H., 1998. Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys. J Comp Neurol. 394, 475-495.

Hailstone, J.C., Crutch, S.J., Vestergaard, M.D., Patterson, R.D., Warren, J.D., 2010. Progressive associative phonagnosia: a neuropsychological analysis. Neuropsychologia. 48, 1104-1114.

Hailstone, J.C., Omar, R., Warren, J.D., 2009. Relatively preserved knowledge of music in semantic dementia. J Neurol Neurosurg Psychiatry. 80, 808-809.

Hall, D.A., Plack, C.J., 2009. Pitch processing sites in the human auditory brain. Cereb Cortex. 19, 576-585.

Halpern, A.R., Zatorre, R.J., Bouffard, M., Johnson, J.A., 2004. Behavioral and neural correlates of perceived and imagined musical timbre. Neuropsychologia. 42, 1281-1292.

Hassabis, D., Maguire, E.A., 2007. Deconstructing episodic memory with construction. Trends Cogn Sci. 11, 299-306.

Hattiangadi, N., Pillion, J.P., Slomine, B., Christensen, J., Trovato, M.K., Speedie, L.J., 2005. Characteristics of auditory agnosia in a child with severe traumatic brain injury: a case report. Brain Lang. 92, 12-25.

Hellstrom, A., Almkvist, O., 1997. Tone duration discrimination in demented, memory-impaired, and healthy elderly. Dement Geriatr Cogn Disord. 8, 49-54.

Henson, R.N., Gagnepain, P., 2010. Predictive, interactive multiple memory systems. Hippocampus. 20, 1315-1326.

Hillis, A.E., Caramazza, A., 1991. Category-specific naming and comprehension impairment: a double dissociation. Brain. 114, 2081-2094.

Hodges, J.R., Patterson, K., 2007. Semantic dementia: a unique clinicopathological syndrome. Lancet Neurol. 6, 1004-1014.

Hodges, J.R., Salmon, D.P., Butters, N., 1992. Semantic memory impairment in Alzheimer's disease: failure of access or degraded knowledge? Neuropsychologia. 30, 301-314.

Hovius, M., Kellenbach, M.L., Graham, K.S., Hodges, J.R., Patterson, K., 2003. What does the object decision task measure? Reflections on the basis of evidence from semantic dementia. Neuropsychology. 17, 100-107.

Hu, W.T., McMillan, C., Libon, D., Leight, S., Forman, M., Lee, V.M., Trojanowski, J.Q., Grossman, M., 2010. Multi-modal predictors for Alzheimer disease in nonfluent primary progressive aphasia. Neurology. 75, 595-602.

Humphries, C., Liebenthal, E., Binder, J.R., 2010. Tonotopic organization of human auditory cortex. Neuroimage. 50, 1202-1211.

Hyde, K.L., Zatorre, R.J., Peretz, I., 2011. Functional MRI Evidence of an Abnormal Neural Network for Pitch Processing in Congenital Amusia. Cereb Cortex. 21, 292-9.

Hyde, K.L., Lerch, J.P., Zatorre, R.J., Griffiths, T.D., Evans, A.C., Peretz, I., 2007. Cortical thickness in congenital amusia: when less is better than more. J Neurosci. 27, 13028-13032.

Hyde, K.L., Zatorre, R.J., Griffiths, T.D., Lerch, J.P., Peretz, I., 2006. Morphometry of the amusic brain: a two-site study. Brain. 129, 2562-2570.

Hyde, K.L., Peretz, I., 2004. Brains that are out of tune but in time. Psychol Sci. 15, 356-360.

Iizuka, O., Suzuki, K., Endo, K., Fujii, T., Mori, E., 2007. Pure word deafness and pure anarthria in a patient with frontotemporal dementia. Eur J Neurol. 14, 473-475.

Ikeda, M., Patterson, K., Graham, K.S., Ralph, M.A., Hodges, J.R., 2006. A horse of a different colour: do patients with semantic dementia recognise different versions of the same object as the same? Neuropsychologia. 44, 566-575.

Jackson, M., Warrington, E.K., 1986. Arithmetic skills in patients with unilateral cerebral lesions. Cortex. 22, 611-620.

Jeon, H.A., Lee, K.M., 2009. Diagnostic utility of sound naming in early Alzheimer's disease. J Int Neuropsychol Soc. 15, 231-238.

Johnsrude, I.S., Penhune, V.B., Zatorre, R.J., 2000. Functional specificity in the right human auditory cortex for perceiving pitch direction. Brain. 123, 155-163.

Jorgens, S., Biermann-Ruben, K., Kurz, M.W., Flugel, C., Daehli Kurz, K., Antke, C., Hartung, H.P., Seitz, R.J., Schnitzler, A., 2008. Word deafness as a cortical auditory processing deficit: a case report with MEG. Neurocase. 14, 307-316.

Joubert, S., Brambati, S.M., Ansado, J., Barbeau, E.J., Felician, O., Didic, M., Lacombe, J., Goldstein, R., Chayer, C., Kergoat, M.J., 2010. The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. Neuropsychologia. 48, 978-988.

Kaas, J.H., Hackett, T.A., 2000. Subdivisions of auditory cortex and processing streams in primates. Proc Natl Acad Sci USA. 97, 11793-11799.

Kaas, J.H., Hackett, T.A., 1999. 'What' and 'where' processing in auditory cortex. Nat Neurosci. 2, 1045-1047.

Kaga K., Nakamura M., Takayama Y., Momose H., 2004. A case of cortical deafness and anarthria. Acta Otolaryngol. 124, 202-5.

Kay, J., Lesser, R., Coltheart, M., 1992. Psycholinguistic assessments of language processing in aphasia (PALPA). Lawrence Erlbaum Associates, Hove.

Kawahara, H., Irino, T., 2005. Underlying Principles of a High-quality Speech Manipulation System STRAIGHT and Its Application to Speech Segregation. In: Divenyi, P. (Ed.), Speech Separation by Humans and Machines. Springer US, pp. 167-180.

Kawahara, H., Masuda-Katsuse, I., de Cheveigne, A., 1999. Restructuring speech representations using a pitch-adaptive time-frequency smoothing and an instantaneous-frequency-based F0 extraction: Possible role of a repetitive structure in sounds. Speech Communication. 27, 187-207.

Kipps, C.M., Hodges, J.R., 2007. Frontotemporal Dementia Syndromes. In: Growdon, J.H., Rossor, M.N. (Eds.), The Dementias 2. Butterworth-Heinemann, Philadelphia, pp. 112-140.

Klemen, J., Buchel, C., Rose, M., 2009. Perceptual load interacts with stimulus processing across sensory modalities. Eur J Neurosci. 29, 2426-2434.

Koelsch, S., Schulze, K., Sammler, D., Fritz, T., Muller, K., Gruber, O., 2009. Functional architecture of verbal and tonal working memory: an FMRI study. Hum Brain Mapp. 30, 859-873.

Kohlmetz, C., Muller, S.V., Nager, W., Munte, T.F., Altenmuller, E., 2003. Selective loss of timbre perception for keyboard and percussion instruments following a right temporal lesion. Neurocase. 9, 86-93.

Kohn, S.E., Friedman, R.B., 1986. Word-meaning deafness: A phonological-semantic dissociation. Cognitive Neuropsychology. 3, 291-308.

Kosaki, H., Hashikawa, T., He, J., Jones, E.G., 1997. Tonotopic organization of auditory cortical fields delineated by parvalbumin immunoreactivity in macaque monkeys. J Comp Neurol. 386, 304-316.

Kowalski, N., Depireux, D.A., Shamma, S.A., 1996. Analysis of dynamic spectra in ferret primary auditory cortex. I. Characteristics of single-unit responses to moving ripple spectra. J Neurophysiol. 76, 3503-3523.

Kubovy, M., Van Valkenburg, D., 2001. Auditory and visual objects. Cognition. 80, 97-126.

Kumar, S., Stephan, K.E., Warren, J.D., Friston, K.J., Griffiths, T.D., 2007. Hierarchical processing of auditory objects in humans. PLoS Comput Biol. 3, e100.

Kurylo, D.D., Corkin, S., Allard, T., Zatorre, R.J., Growdon, J.H., 1993. Auditory function in Alzheimer's disease. Neurology. 43, 1893-1899.

Kusmierek, P., Rauschecker, J.P., 2009. Functional specialization of medial auditory belt cortex in the alert rhesus monkey. J Neurophysiol. 102, 1606-1622.

Lambon Ralph, M.A., Sage, K., Jones, R.W., Mayberry, E.J., 2010. Coherent concepts are computed in the anterior temporal lobes. Proc Natl Acad Sci USA. 107, 2717-2722.

Leaver, A.M., Rauschecker, J.P., 2010. Cortical representation of natural complex sounds: effects of acoustic features and auditory object category. J Neurosci. 30, 7604-7612.

Lechevalier, B., Platel, H., Eustache, F., 1995. [Neuropsychology of musical identification]. Rev Neurol (Paris). 151, 505-510.

Lechevalier, B., Rossa, Y., Eustache, F., Schupp, C., Boner, L., Bazin, C., 1984. [Case of cortical deafness sparing the music area]. Rev Neurol (Paris). 140, 190-201.

Lee, C.C., Winer, J.A., 2008. Connections of cat auditory cortex: III. Corticocortical system. J Comp Neurol. 507, 1920-1943.

Leech, R., Gygi, B., Aydelott, J., Dick, F., 2009. Informational factors in identifying environmental sounds in natural auditory scenes. J Acoust Soc Am. 126, 3147-3155.

Lewis, J.W., Talkington, W.J., Puce, A., Engel, L.R., Frum, C., 2010. Cortical Networks Representing Object Categories and High-level Attributes of Familiar Real-world Action Sounds. J Cogn Neurosci. [Epub ahead of print]

Lewis, J.W., Talkington, W.J., Walker, N.A., Spirou, G.A., Jajosky, A., Frum, C., Brefczynski-Lewis, J.A., 2009. Human cortical organization for processing vocalizations indicates representation of harmonic structure as a signal attribute. J Neurosci. 29, 2283-2296.

Lewis, J.W., Phinney, R.E., Brefczynski-Lewis, J.A., DeYoe, E.A., 2006. Lefties get it "right" when hearing tool sounds. J Cogn Neurosci 18, 1314-1330.

Lewis, J.W., Brefczynski, J.A., Phinney, R.E., Janik, J.J., DeYoe, E.A., 2005. Distinct cortical pathways for processing tool versus animal sounds. J Neurosci. 25, 5148-5158.

Liu, F., Patel, A.D., Fourcin, A., Stewart, L., 2010. Intonation processing in congenital amusia: discrimination, identification and imitation. Brain. 133, 1682-1693.

Liu, X.Z., Yan, D., 2007. Ageing and hearing loss. J Pathol. 211, 188-197.

Luzzi, S., Snowden, J.S., Neary, D., Coccia, M., Provinciali, L., Lambon Ralph, M.A., 2007. Distinct patterns of olfactory impairment in Alzheimer's disease, semantic dementia, frontotemporal dementia, and corticobasal degeneration. Neuropsychologia. 45, 1823-1831.

Lyzenga, J., Carlyon, R.P., Moore, B.C., 2004. The effects of real and illusory glides on pure-tone frequency discrimination. J Acoust Soc Am. 116, 491-501.

Marinkovic, K., Dhond, R.P., Dale, A.M., Glessner, M., Carr, V., Halgren, E., 2003. Spatiotemporal dynamics of modality-specific and supramodal word processing. Neuron. 38, 487-497.

Marr, D., 1982. Vision: a computational investigation into the human representation and processing of visual information. W.H. Freeman, San Francisco.

Martin, A., 2007. The representation of object concepts in the brain. Annu Rev Psychol. 58, 25-45.

Martin, A., Chao, L.L., 2001. Semantic memory and the brain: structure and processes. Curr Opin Neurobiol. 11, 194-201.

Martin, A., Haxby, J.V., Lalonde, F.M., Wiggs, C.L., Ungerleider, L.G., 1995. Discrete cortical regions associated with knowledge of color and knowledge of action. Science. 270, 102-105.

Mayberry, E.J., Sage, K., Lambon Ralph, M.A., 2010. At the Edge of Semantic Space: The Breakdown of Coherent Concepts in Semantic Dementia Is Constrained by Typicality and Severity but Not Modality. J Cogn Neurosci. [Epub ahead of print]

Mazzucchi, A., Marchini, C., Budai, R., Parma, M., 1982. A case of receptive amusia with prominent timbre perception defect. J Neurol Neurosurg Psychiatry. 45, 644-647.

McCarthy, R., Warrington, E.K., 1984. A two-route model of speech production. Evidence from aphasia. Brain. 107, 463-485.

McKenna, P., Parry, R., 1994. Category specificity in the naming of natural and man-made objects: Normative data from adults and children. Neuropsychological Rehabilitation. 4, 225-281.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 34, 939-944.

Mendelson, J.R., Schreiner, C.E., Sutter, M.L., Grasse, K.L., 1993. Functional topography of cat primary auditory cortex: responses to frequency-modulated sweeps. Exp Brain Res. 94, 65-87.

Mendez, M.F., Mendez, M.A., Martin, R., Smyth, K.A., Whitehouse, P.J., 1990. Complex visual disturbances in Alzheimer's disease. Neurology. 40, 439-443.

Mendez, M.F., Geehan, G.R.Jr., 1988. Cortical auditory disorders: clinical and psychoacoustic features. J Neurol Neurosurg Psychiatry. 51, 1-9.

Mesulam, M., 2009. Defining neurocognitive networks in the BOLD new world of computed connectivity. Neuron. 62, 1-3.

Metz-Lutz, M.N., Dahl, E., 1984. Analysis of word comprehension in a case of pure word deafness. Brain Lang. 23, 13-25.

Miceli, G., 1982. The processing of speech sounds in a patient with cortical auditory disorder. Neuropsychologia. 20, 5-20.

Mohedano-Moriano, A., Martinez-Marcos, A., Pro-Sistiaga, P., Blaizot, X., Arroyo-Jimenez, M.M., Marcos, P., Artacho-Perula, E., Insausti, R., 2008. Convergence of unimodal and polymodal sensory input to the entorhinal cortex in the fascicularis monkey. Neuroscience. 151, 255-271.

Mohs, R.C., Knopman, D., Petersen, R.C., Ferris, S.H., Ernesto, C., Grundman, M., Sano, M., Bieliauskas, L., Geldmacher, D., Clark, C., Thal, L.J., 1997. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 11, S13-S21.

Moore, B.C.J., Gockel, H., 2002. Factors Influencing Sequential Stream Segregation. Acta Acustica. 88, 320-333.

Moss, M.B., Albert, M.S., Butters, N., Payne, M., 1986. Differential patterns of memory loss among patients with Alzheimer's disease, Huntington's disease, and alcoholic Korsakoff's syndrome. Arch Neurol. 43, 239-246.

Mummery, C.J., Patterson, K., Wise, R.J., Vandenberghe, R., Price, C.J., Hodges, J.R., 1999. Disrupted temporal lobe connections in semantic dementia. Brain. 122, 61-73.

Munoz-Lopez, M.M., Mohedano-Moriano, A., Insausti, R., 2010. Anatomical pathways for auditory memory in primates. Front Neuroanat. 4, 129.

Murray, E.A., Bussey, T.J., 1999. Perceptual-mnemonic functions of the perirhinal cortex. Trends Cogn Sci. 3, 142-151.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F., 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 51, 1546-1554.

Nebes, R.D., 1989. Semantic memory in Alzheimer's disease. Psychol Bull. 106, 377-394.

Nelken, I., Bar-Yosef, O., 2008. Neurons and objects: the case of auditory cortex. Front Neurosci. 2, 107-113.

Neuner, F., Schweinberger, S.R., 2000. Neuropsychological impairments in the recognition of faces, voices, and personal names. Brain Cogn. 44, 342-366.

Omar, R., Hailstone, J.C., Warren, J.E., Crutch, S.J., Warren, J.D., 2010. The cognitive organization of music knowledge: a clinical analysis. Brain. 133, 1200-1213.

Op de Beeck, H.P., Haushofer, J., Kanwisher, N.G., 2008. Interpreting fMRI data: maps, modules and dimensions. Nat Rev Neurosci. 9, 123-135.

Otsuki, M., Soma, Y., Sato, M., Homma, A., Tsuji, S., 1998. Slowly progressive pure word deafness. Eur Neurol. 39, 135-140.

Overath, T., Kumar, S., Stewart, L., von, K.K., Cusack, R., Rees, A., Griffiths, T.D., 2010. Cortical mechanisms for the segregation and representation of acoustic textures. J Neurosci. 30, 2070-2076.

Patterson, K., Nestor, P.J., Rogers, T.T., 2007. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci. 8, 976-987.

Patterson, R.D., Uppenkamp, S., Johnsrude, I.S., Griffiths, T.D., 2002. The processing of temporal pitch and melody information in auditory cortex. Neuron. 36, 767-776.

Penagos, H., Melcher, J.R., Oxenham, A.J., 2004. A neural representation of pitch salience in nonprimary human auditory cortex revealed with functional magnetic resonance imaging. J Neurosci. 24, 6810-6815.

Peretz, I., Brattico, E., Jarvenpaa, M., Tervaniemi, M., 2009. The amusic brain: in tune, out of key, and unaware. Brain. 132, 1277-1286.

Peretz, I., Zatorre, R.J., 2005. Brain organization for music processing. Annu Rev Psychol 56, 89-114.

Peretz, I., Coltheart, M., 2003. Modularity of music processing. Nat Neurosci. 6, 688-691.

Peretz, I., 1996. Can We Lose Memory for Music? A Case of Music Agnosia in a Nonmusician. Journal of Cognitive Neuroscience. 8, 481-496.

Peretz, I., Kolinsky, R., Tramo, M., Labrecque, R., Hublet, C., Demeurisse, G., Belleville, S., 1994. Functional dissociations following bilateral lesions of auditory cortex. Brain 117 (Pt 6), 1283-1301.

Petkov, C.I., Kayser, C., Augath, M., Logothetis, N.K., 2006. Functional imaging reveals numerous fields in the monkey auditory cortex. PLoS Biol. 4, e215.

Phillips, D.P., Semple, M.N., Calford, M.B., Kitzes, L.M., 1994. Level-dependent representation of stimulus frequency in cat primary auditory cortex. Exp Brain Res. 102, 210-226.

Plasencia, P.M., Dorado, J.I., Serrano Rodriguez, J.M., Sellan, C., 2006. Neuropsychological evidence for "word-meaning deafness" in a Spanish-speaking patient. Brain Lang. 97, 214-218.

Plaut, D.C., 1995. Double dissociation without modularity: evidence from connectionist neuropsychology. J Clin Exp Neuropsychol. 17, 291-321.

Plaut, D.C., Shallice, T., 1993. Deep dyslexia: A case study of connectionist neuropsychology. Cognitive Neuropsychology. 10, 377-500.

Pobric, G., Jefferies, E., Lambon Ralph, M.A., 2010a. Amodal semantic representations depend on both anterior temporal lobes: evidence from repetitive transcranial magnetic stimulation. Neuropsychologia. 48, 1336-1342.

Pobric, G., Jefferies, E., Lambon Ralph, M.A., 2010b. Category-specific versus category-general semantic impairment induced by transcranial magnetic stimulation. Curr Biol. 20, 964-968.

Pobric, G., Jefferies, E., Lambon Ralph, M.A., 2007. Anterior temporal lobes mediate semantic representation: mimicking semantic dementia by using rTMS in normal participants. Proc Natl Acad Sci USA. 104, 20137-20141.

Poeppel, D., 2003. The analysis of speech in different temporal integration windows: cerebral lateralization as asymmetric sampling in time. Speech Communication. 41, 245-255.

Poremba, A., Saunders, R.C., Crane, A.M., Cook, M., Sokoloff, L., Mishkin, M., 2003. Functional mapping of the primate auditory system. Science. 299, 568-572.

Praamstra, P., Hagoort, P., Maassen, B., Crul, T., 1991. Word deafness and auditory cortical function. A case history and hypothesis. Brain. 114, 1197-1225.

Price, C.J., Friston, K.J., 2002. Functional imaging studies of neuropsychological patients: applications and limitations. Neurocase. 8, 345-354.

Protzner, A.B., Cortese, F., Alain, C., McIntosh, A.R., 2009. The temporal interaction of modality specific and process specific neural networks supporting simple working memory tasks. Neuropsychologia. 47, 1954-1963.

Protzner, A.B., McIntosh, A.R., 2007. The interplay of stimulus modality and response latency in neural network organization for simple working memory tasks. J Neurosci. 27, 3187-3197.

Pulvermüller, F., Cooper-Pye, E., Dine, C., Hauk, O., Nestor, P.J., Patterson, K., 2010. The word processing deficit in semantic dementia: all categories are equal, but some categories are more equal than others. J Cogn Neurosci. 22, 2027-2041.

Pulvermüller, F., 2005. Brain mechanisms linking language and action. Nat Rev Neurosci. 6, 576-582.

Rama, P., Courtney, S.M., 2005. Functional topography of working memory for face or voice identity. Neuroimage. 24, 224-234.

Rapcsak, S.Z., Kentros, M., Rubens, A.B., 1989. Impaired recognition of meaningful sounds in Alzheimer's disease. Arch Neurol. 46, 1298-1300.

Rauschecker, J.P., Scott, S.K., 2009. Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. Nat Neurosci. 12, 718-724.

Rauschecker, J.P., Tian, B., 2004. Processing of band-passed noise in the lateral auditory belt cortex of the rhesus monkey. J Neurophysiol. 91, 2578-2589.

Rauschecker, J.P., Tian, B., 2000. Mechanisms and streams for processing of "what" and "where" in auditory cortex. Proc Natl Acad Sci USA. 97, 11800-11806.

Rauschecker, J.P., 1998. Cortical processing of complex sounds. Curr Opin Neurobiol. 8, 516-521.

Rauschecker, J.P., Tian, B., Hauser, M., 1995. Processing of complex sounds in the macaque nonprimary auditory cortex. Science. 268, 111-114.

Raven, J., Raven, J.C., Court, J.H., 2003. Manual for Raven's Progressive Matrices and Vocabulary Scales. Harcourt Assessment, San Antonio, TX.

Read, H.L., Winer, J.A., Schreiner, C.E., 2001. Modular organization of intrinsic connections associated with spectral tuning in cat auditory cortex. Proc Natl Acad Sci USA. 98, 8042-8047.

Recanzone, G.H., Schreiner, C.E., Sutter, M.L., Beitel, R.E., Merzenich, M.M., 1999. Functional organization of spectral receptive fields in the primary auditory cortex of the owl monkey. J Comp Neurol. 415, 460-481.

Reitan, R.M., 1992. Trail making test: manual for administration and scoring. Reitan Neuropsychology Laboratory, Tucson, Arizona.

Riddoch, M.J., Humphreys, G.W., 1987. A case of integrative visual agnosia. Brain. 110 (Pt 6), 1431-1462.

Riddoch, M.J., Humphreys, G.W., Akhtar, N., Allen, H., Bracewell, R.M., Schofield, A.J., 2008. A tale of two agnosias: distinctions between form and integrative agnosia. Cogn Neuropsychol. 25, 56-92.

Ridgway, G.R., Omar, R., Ourselin, S., Hill, D.L., Warren, J.D., Fox, N.C., 2009. Issues with threshold masking in voxel-based morphometry of atrophied brains. NeuroImage. 44: 99-111.

Rochon, E., Waters, G.S., Caplan, D., 2000. The relationship between measures of working memory and sentence comprehension in patients with Alzheimer's disease. J Speech Lang Hear Res. 43, 395-413.

Rogers, T.T., Lambon Ralph, M.A., Garrard, P., Bozeat, S., McClelland, J.L., Hodges, J.R., Patterson, K., 2004. Structure and deterioration of semantic memory: a neuropsychological and computational investigation. Psychol Rev. 111, 205-235.

Rogers, T.T., McClelland, J.L., 2004. Semantic cognition: a parallel distributed processing approach. The MIT Press, Cambridge, MA.

Rohrer, J.D., Crutch, S.J., Warrington, E.K., Warren, J.D., 2010a. Progranulin-associated primary progressive aphasia: a distinct phenotype? Neuropsychologia. 48, 288-297.

Rohrer, J.D., Ridgway, G.R., Crutch, S.J., Hailstone, J., Goll, J.C., Clarkson, M.J., Mead, S., Beck, J., Mummery, C., Ourselin, S., Warrington, E.K., Rossor, M.N., Warren, J.D., 2010b. Progressive logopenic/phonological aphasia: erosion of the language network. Neuroimage. 49, 984-993.

Rohrer, J.D., Rossor, M.N., Warren, J.D., 2010c. Syndromes of nonfluent primary progressive aphasia: a clinical and neurolinguistic analysis. Neurology. 75, 603-610.

Rohrer, J.D., Rossor, M.N., Warren, J.D., 2010d. Alzheimer's pathology in primary progressive aphasia. Neurobiol Aging. [Epub ahead of print]

Rohrer, J.D., Warren, J.D., Modat, M., Ridgway, G.R., Douiri, A., Rossor, M.N., Ourselin, S., Fox, N.C., 2009. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. Neurology. 72, 1562-1569.

Romanski, L.M., Averbeck, B.B., 2009. The primate cortical auditory system and neural representation of conspecific vocalizations. Annu Rev Neurosci. 32, 315-46.

Romanski, L.M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P.S., Rauschecker, J.P., 1999. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. Nat Neurosci. 2, 1131-1136.

Rossor, M., Collinge, J., Fox, N., Howard, R., Mallucci, G., Mummery, C., Warren, J., 2010. Cognitive Impairment and Dementia. In: Clarke, C., Howard, R., Shorvon, S., Rossor, M. (Eds.), Neurology: A Queen Square Textbook. Wiley-Blackwell, Oxford, pp. 245-288.

Rumelhart, D.E., Hinton, G.E., Williams, R.J., 1986. Learning representations by back-propagating errors. Nature. 323, 533-536.

Saffran, E.M., Marin, O.S., Yeni-Komshian, G.H., 1976. An analysis of speech perception in word deafness. Brain Lang. 3, 209-228.

Salami, A., Eriksson, J., Kompus, K., Habib, R., Kauppi, K., Nyberg, L., 2010. Characterizing the neural correlates of modality-specific and modality-independent accessibility and availability signals in memory using partial-least squares. Neuroimage. 52, 686-698.

Samson, S., Zatorre, R.J., Ramsay, J.O., 2002. Deficits of musical timbre perception after unilateral temporal-lobe lesion revealed with multidimensional scaling. Brain. 125, 511-523.

Samson, S., Zatorre, R.J., 1994. Contribution of the right temporal lobe to musical timbre discrimination. Neuropsychologia. 32, 231-240.

Sauter, D.A., Eisner, F., Calder, A.J., Scott, S.K., 2010. Perceptual cues in non-verbal vocal expressions of emotion. Q J Exp Psychol. 63, 2251-2272.

Sauter, D., Scott, S., 2007. More than one kind of happiness: Can we recognize vocal expressions of different positive states? Motivation and Emotion. 31, 192-199.

Saygin, A.P., Leech, R., Dick, F., 2010. Non-verbal auditory agnosia with lesion to Wernicke's area. Neuropsychologia. 48, 107-113.

Saygin, A.P., Dick, F., Wilson, S.M., Dronkers, N.F., Bates, E., 2003. Neural resources for processing language and environmental sounds: evidence from aphasia. Brain. 126, 928-945.

Saykin, A.J., Flashman, L.A., Frutiger, S.A., Johnson, S.C., Mamourian, A.C., Moritz, C.H., O'Jile, J.R., Riordan, H.J., Santulli, R.B., Smith, C.A., Weaver, J.B., 1999. Neuroanatomic substrates of semantic memory impairment in Alzheimer's disease: patterns of functional MRI activation. J Int Neuropsychol Soc. 5, 377-392.

Schadwinkel, S., Gutschalk, A., 2010. Activity Associated with Stream Segregation in Human Auditory Cortex is Similar for Spatial and Pitch Cues. Cereb Cortex. 20, 2863-2873.

Schebesch, G., Lingner, A., Firzlaff, U., Wiegrebe, L., Grothe, B., 2010. Perception and neural representation of size-variant human vowels in the Mongolian gerbil (Meriones unguiculatus). Hear Res. 261, 1-8.

Schneider, P., Sluming, V., Roberts, N., Scherg, M., Goebel, R., Specht, H.J., Dosch, H.G., Bleeck, S., Stippich, C., Rupp, A., 2005. Structural and functional asymmetry of lateral Heschl's gyrus reflects pitch perception preference. Nat Neurosci. 8, 1241-1247.

Schnider, A., Benson, D.F., Alexander, D.N., Schnider-Klaus, A., 1994. Non-verbal environmental sound recognition after unilateral hemispheric stroke. Brain. 117 (Pt 2), 281-287.

Schonell, F.J., Schonell, P.E., 1960. Diagnostic and attainment testing. Oliver and Boyd, Edinburgh.

Schönwiesner, M., Novitski, N., Pakarinen, S., Carlson, S., Tervaniemi, M., Naatanen, R., 2007. Heschl's gyrus, posterior superior temporal gyrus, and mid-ventrolateral prefrontal cortex have different roles in the detection of acoustic changes. J Neurophysiol 97, 2075-2082

Schönwiesner, M., Rubsamen, R., von Cramon, D.Y., 2005. Hemispheric asymmetry for spectral and temporal processing in the human antero-lateral auditory belt cortex. Eur J Neurosci. 22, 1521-1528.

Schreiner, C.E., Winer, J.A., 2007. Auditory cortex mapmaking: principles, projections, and plasticity. Neuron. 56, 356-365.

Schreiner, C.E., Read, H.L., Sutter, M.L., 2000. Modular organization of frequency integration in primary auditory cortex. Annu Rev Neurosci. 23:501-29.

Schreiner, C.E., Mendelson, J.R., 1990. Functional topography of cat primary auditory cortex: distribution of integrated excitation. .Neurophysiol. 64, 1442-1459.

Schroeter, M.L., Raczka, K., Neumann, J., Yves von, C.D., 2007. Towards a nosology for frontotemporal lobar degenerations-a meta-analysis involving 267 subjects. Neuroimage. 36, 497-510.

Schulze, K., Mueller, K., Koelsch, S., 2011. Neural correlates of strategy use during auditory working memory in musicians and non-musicians. Eur J Neurosci. 33, 189-196.

Schulze, K., Zysset, S., Mueller, K., Friederici, A.D., Koelsch, S., 2010. Neuroarchitecture of verbal and tonal working memory in nonmusicians and musicians. Human Brain Mapping. 32, 771-83.

Scott, S.K., Blank, C.C., Rosen, S., Wise, R.J., 2000. Identification of a pathway for intelligible speech in the left temporal lobe. Brain. 123 (Pt 12), 2400-2406.

Seeley, W.W., Crawford, R.K., Zhou, J., Miller, B.L., Greicius, M.D., 2009. Neurodegenerative diseases target large-scale human brain networks. Neuron. 62, 42-52.

Sek, A., Moore, B.C., 1999. Discrimination of frequency steps linked by glides of various durations. J Acoust Soc Am. 106, 351-359.

Shallice, T., 1988. From neuropsychology to mental structure. Cambridge University Press, Cambridge.

Silveri, M.C., Gainotti, G., 1988. Interaction between vision and language in category-specific semantic impairment. Cognitive Neuropsychology. 5, 677-709.

Simons, J.S., Lambon Ralph, M.A., 1999. The auditory agnosias. Neurocase. 5, 379-406.

Singh, N.C., Theunissen, F.E., 2003. Modulation spectra of natural sounds and ethological theories of auditory processing. J Acoust Soc Am. 114, 3394-3411.

Smith, D.R., Patterson, R.D., 2005. The interaction of glottal-pulse rate and vocal-tract length in judgements of speaker size, sex, and age. J Acoust Soc Am. 118, 3177-3186.

Smith, D.R., Patterson, R.D., Turner, R., Kawahara, H., Irino, T., 2005. The processing and perception of size information in speech sounds. J Acoust Soc Am. 117, 305-318.

Smith, K.R., Hsieh, I.H., Saberi, K., Hickok, G., 2010. Auditory spatial and object processing in the human planum temporale: no evidence for selectivity. J Cogn Neurosci. 22, 632-639.

Snyder, J.S., Alain, C., 2007. Toward a neurophysiological theory of auditory stream segregation. Psychol Bull. 133, 780-799.

Sonty, S.P., Mesulam, M.M., Weintraub, S., Johnson, N.A., Parrish, T.B., Gitelman, D.R., 2007. Altered effective connectivity within the language network in primary progressive aphasia. J Neurosci. 27, 1334-1345.

Soto-Faraco, S., Spence, C., 2002. Modality-specific auditory and visual temporal processing deficits. Q J Exp Psychol A. 55, 23-40.

Spreen , O., Benton , A.L., Fincham , R.W., 1965. Auditory agnosia without aphasia. Arch Neurol. 13, 84-92.

Staeren, N., Renvall, H., De Martino, F., Goebel, R., Formisano, E., 2009. Sound categories are represented as distributed patterns in the human auditory cortex. Curr Biol. 19, 498-502.

Stefanatos, G.A., Gershkoff, A., Madigan, S., 2005. On pure word deafness, temporal processing, and the left hemisphere. J Int Neuropsychol Soc. 11, 456-470.

Stewart, L., von Kriegstein, K., Warren, J.D., Griffiths, T.D., 2006. Music and the brain: disorders of musical listening. Brain. 129, 2533-2553.

Storey, E., Slavin, M.J., Kinsella, G.J., 2002. Patterns of cognitive impairment in Alzheimer's disease: assessment and differential diagnosis. Front Biosci. 7, e155-84.

Tanaka, Y., Yamadori, A., Mori, E., 1987. Pure word deafness following bilateral lesions. A psychophysical analysis. Brain 110 (Pt 2), 381-403.

Taylor, A., Warrington, E.K., 1971. Visual agnosia: a single case report. Cortex. 7, 152-161.

Teki, S., Grube, M., Kumar, S., Griffiths, T.D., 2011. Distinct neural substrates of duration-based and beat-based auditory timing. J Neurosci. 31, 3805-3812.

Terao, Y., Mizuno, T., Shindoh, M., Sakurai, Y., Ugawa, Y., Kobayashi, S., Nagai, C., Furubayashi, T., Arai, N., Okabe, S., Mochizuki, H., Hanajima, R., Tsuji, S., 2006. Vocal amusia in a professional tango singer due to a right superior temporal cortex infarction. Neuropsychologia. 44, 479-488.

Testa, J.A., Beatty, W.W., Gleason, A.C., Orbelo, D.M., Ross, E.D., 2001. Impaired affective prosody in AD: relationship to aphasic deficits and emotional behaviors. Neurology. 57, 1474-1481.

Thompson-Schill, S.L., Gabrieli, J.D., Fleischman, D.A., 1999. Effects of structural similarity and name frequency on picture naming in Alzheimer's disease. J Int Neuropsychol Soc. 5, 659-667.

Tillmann, B., Schulze, K., Foxton, J.M., 2009. Congenital amusia: a short-term memory deficit for non-verbal, but not verbal sounds. Brain Cogn. 71, 259-264.

Tourville, J.A., Reilly, K.J., Guenther, F.H., 2008. Neural mechanisms underlying auditory feedback control of speech. Neuroimage. 39, 1429-1443.

Tramo, M.J., Shah, G.D., Braida, L.D., 2002. Functional role of auditory cortex in frequency processing and pitch perception. J Neurophysiol. 87, 122-139.

Tranel, D., Damasio, H., Damasio, A.R., 1997. A neural basis for the retrieval of conceptual knowledge. Neuropsychologia. 35, 1319-1327.

Tyler, L.K., Stamatakis, E.A., Bright, P., Acres, K., Abdallah, S., Rodd, J.M., Moss, H.E., 2004. Processing objects at different levels of specificity. J Cogn Neurosci. 16, 351-362.

Tyler, L.K., Moss, H.E., 2001. Towards a distributed account of conceptual knowledge. Trends Cogn Sci. 5, 244-252.

Uhlhaas, P.J., Pantel, J., Lanfermann, H., Prvulovic, D., Haenschel, C., Maurer, K., Linden, D.E., 2008. Visual perceptual organization deficits in Alzheimer's dementia. Dement Geriatr Cogn Disord. 25, 465-475.

Uttner, I., Mottaghy, F.M., Schreiber, H., Riecker, A., Ludolph, A.C., Kassubek, J., 2006. Primary progressive aphasia accompanied by environmental sound agnosia: a neuropsychological, MRI and PET study. Psychiatry Res. 146, 191-197.

van Dinther, R., Patterson, R.D., 2006. Perception of acoustic scale and size in musical instrument sounds. J Acoust Soc Am. 120, 2158-2176.

van Drongelen, W., 2007. Signal processing for neuroscientists: introduction to the analysis of physiological signals. Elsevier/Academic Press, Amsterdam; Boston.

Van Lancker, D.R., Kreiman, J., Cummings, J., 1989. Voice perception deficits: neuroanatomical correlates of phonagnosia. J Clin Exp Neuropsychol. 11, 665-674.

Van Lancker, D.R., Cummings, J.L., Kreiman, J., Dobkin, B.H., 1988. Phonagnosia: a dissociation between familiar and unfamiliar voices. Cortex. 24, 195-209.

Van Lancker, D., Kreiman, J., 1987. Voice discrimination and recognition are separate abilities. Neuropsychologia. 25, 829-834.

Vanstone, A.D., Cuddy, L.L., 2010. Musical memory in Alzheimer disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 17, 108-128.

Vignolo, L.A., 2003. Music agnosia and auditory agnosia. Dissociations in stroke patients. Ann NY Acad Sci. 999, 50-57.

Vignolo, L.A., 1982. Auditory agnosia. Philos Trans R Soc Lond B Biol Sci. 298, 49-57.

Visser, M., Lambon Ralph, M.A., 2011. Differential Contributions of Bilateral Ventral Anterior Temporal Lobe and Left Anterior Superior Temporal Gyrus to Semantic Processes. J Cogn Neurosci. [Epub ahead of print]

Visser, M., Embleton, K.V., Jefferies, E., Parker, G.J., Lambon Ralph, M.A., 2010a. The inferior, anterior temporal lobes and semantic memory clarified: novel evidence from distortion-corrected fMRI. Neuropsychologia. 48, 1689-1696.

Visser, M., Jefferies, E., Lambon Ralph, M.A., 2010b. Semantic processing in the anterior temporal lobes: a meta-analysis of the functional neuroimaging literature. J Cogn Neurosci. 22, 1083-1094.

von Kriegstein, K., Smith, D.R., Patterson, R.D., Ives, D.T., Griffiths, T.D., 2007. Neural representation of auditory size in the human voice and in sounds from other resonant sources. Curr Biol. 17, 1123-1128.

von Kriegstein, K., Warren, J.D., Ives, D.T., Patterson, R.D., Griffiths, T.D., 2006. Processing the acoustic effect of size in speech sounds. Neuroimage. 32, 368-375.

Wang, X., Bendor, D., 2010. Pitch. In: Rees, A., Palmer, A. (Eds.), The Oxford Handbook of Auditory Science: The Auditory Brain. Oxford University Press, Oxford, pp. 149-172.

Wang, E., Peach, R.K., Xu, Y., Schneck, M., Manry, C., 2000. Perception of dynamic acoustic patterns by an individual with unilateral verbal auditory agnosia. Brain Lang. 73, 442-455.

Warren, J.D., Scott, S.K., Price, C.J., Griffiths, T.D., 2006. Human brain mechanisms for the early analysis of voices. Neuroimage. 31, 1389-1397.

Warren, J.D., Jennings, A.R., Griffiths, T.D., 2005a. Analysis of the spectral envelope of sounds by the human brain. Neuroimage. 24, 1052-1057.

Warren, J.E., Wise, R.J., Warren, J.D., 2005b. Sounds do-able: auditory-motor transformations and the posterior temporal plane. Trends Neurosci. 28, 636-643.

Warren, J.D., Griffiths, T.D., 2003. Distinct mechanisms for processing spatial sequences and pitch sequences in the human auditory brain. J Neurosci. 23, 5799-5804.

Warren, J.D., Zielinski, B.A., Green, G.G., Rauschecker, J.P., Griffiths, T.D., 2002. Perception of sound-source motion by the human brain. Neuron. 34, 139-148.

Warrington, E.K., McKenna, P., Orpwood, L., 1998. Single Word Comprehension: A Concrete and Abstract Word Synonym Test. Neuropsychological Rehabilitation. 8, 143-154.

Warrington, E.K., 1996. The Camden memory tests: manual. Psychology Press, East Sussex, UK.

Warrington, E.K., James, M., 1991. The visual object and space perception battery. Thames Valley Test Company, Bury St. Edmunds.

Warrington, E.K., James, M., 1988. Visual apperceptive agnosia: a clinico-anatomical study of three cases. Cortex. 24, 13-32.

Warrington, E.K., McCarthy, R.A., 1987. Categories of knowledge. Further fractionations and an attempted integration. Brain. 110 (Pt 5), 1273-1296.

Warrington, E.K., James, M., 1986. Visual object recognition in patients with right-hemisphere lesions: axes or features? Perception. 15, 355-366.

Warrington, E.K., Shallice, T., 1984. Category specific semantic impairments. Brain. 107 (Pt 3), 829-854.

Warrington, E.K., McCarthy, R., 1983. Category specific access dysphasia. Brain. 106 (Pt 4), 859-878.

Warrington, E.K., Taylor, A.M., 1978. Two categorical stages of object recognition. Perception. 7, 695-705.

Warrington, E.K., Taylor, A.M., 1973. The contribution of the right parietal lobe to object recognition. Cortex. 9, 152-164.

Warrington, E.K., James, M., 1967. An experimental investigation of facial recognition in patients with unilateral cerebral lesions. Cortex. 3, 317-326.

Wechsler, D., 1999. Wechsler abbreviated scale of intelligence: WASI. Psychological Corporation, Harcourt Brace, San Antonio.

Wechsler, D., 1997. Wechsler memory scale: WMS-III. Psychological Corporation, Harcourt Brace, San Antonio.

Wechsler, D., 1987. Wechsler memory scale - revised. Psychological Corporation, Harcourt Brace, San Antonio.

Wessinger, C.M., Van Meter, J., Tian, B., Van Lare, J., Pekar, J., Rauschecker, J.P., 2001. Hierarchical organization of the human auditory cortex revealed by functional magnetic resonance imaging. J Cogn Neurosci. 13, 1-7.

Whitfield, I.C., Evans, E.F., 1965. Responses of auditory cortical neurons to stimuli of changing frequency. J Neurophysiol. 28, 655-72.

Whitwell, J.L., Jack, C.R.Jr., 2005. Comparisons between Alzheimer disease, frontotemporal lobar degeneration, and normal aging with brain mapping. Top Magn Reson Imaging. 16, 409-425.

Williamson, V.J., McDonald, C., Deutsch, D., Griffiths, T.D., Stewart, L., 2010. Faster decline of pitch memory over time in congenital amusia. Adv Cogn Psychol. 6, 15-22.

Williamson, V.J., Stewart, L., 2010. Memory for pitch in congenital amusia: beyond a fine-grained pitch discrimination problem. Memory. 18, 657-669.

Wilson, E.C., Melcher, J.R., Micheyl, C., Gutschalk, A., Oxenham, A.J., 2007. Cortical FMRI activation to sequences of tones alternating in frequency: relationship to perceived rate and streaming. J Neurophysiol. 97, 2230-2238.

Wilson, S.M., Ogar, J.M., Laluz, V., Growdon, M., Jang, J., Glenn, S., Miller, B.L., Weiner, M.W., Gorno-Tempini, M.L., 2009. Automated MRI-based classification of primary progressive aphasia variants. Neuroimage. 47, 1558-1567.

Winkler, I., Denham, S.L., Nelken, I., 2009. Modeling the auditory scene: predictive regularity representations and perceptual objects. Trends Cogn Sci. 13, 532-540.

Woolley, S.M., Fremouw, T.E., Hsu, A., Theunissen, F.E., 2005. Tuning for spectro-temporal modulations as a mechanism for auditory discrimination of natural sounds. Nat Neurosci. 8, 1371-1379.

Yamamoto T., Kikuchi T., Nagae J., Ogata K., Ogawa M., Kawai M., 2004. Dysprosody associated with environmental auditory sound agnosia in right temporal lobe hypoperfusion - a case report. Rinsho Shinkeigaku. 44, 28-33.

Yaqub, B.A., Gascon, G.G., Al-Nosha, M., Whitaker, H., 1988. Pure word deafness (acquired verbal auditory agnosia) in an Arabic speaking patient. Brain. 111 (Pt 2), 457-466.

Young, E.D., 2010. Level and spectrum. In: Rees, A., Palmer, A.R. (Eds.), The Auditory Brain. Oxford University Press, Oxford, pp. 93-124.

Zaehle, T., Geiser, E., Alter, K., Jancke, L., Meyer, M., 2008. Segmental processing in the human auditory dorsal stream. Brain Res. 1220, 179-190.

Zatorre, R.J., Bouffard, M., Belin, P., 2004. Sensitivity to auditory object features in human temporal neocortex. J Neurosci. 24, 3637-3642.

Zatorre, R.J., Belin, P., 2001. Spectral and temporal processing in human auditory cortex. Cereb Cortex. 11, 946-953.

Zatorre, R.J., 1988. Pitch perception of complex tones and human temporal-lobe function. J Acoust Soc Am. 84, 566-572.

Zhang, L.I., Tan, A.Y., Schreiner, C.E., Merzenich, M.M., 2003. Topography and synaptic shaping of direction selectivity in primary auditory cortex. Nature. 424, 201-205.

Zhou, J., Greicius, M.D., Gennatas, E.D., Growdon, M.E., Jang, J.Y., Rabinovici, G.D., Kramer, J.H., Weiner, M., Miller, B.L., Seeley, W.W., 2010. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. Brain. 133, 1352-1367.

8.4 Division of labour

The work described in this thesis was conducted by JCG in collaboration with other researchers based at the Dementia Research Centre and affiliated institutions. Substantial contributions made by others are detailed below.

Chapter 2 Non-verbal auditory object processing in dementia: study 1
Experimental design: JCG, JW, SC
Construction of tests, including automation in MATLAB: JCG
Data collection: JCG; auditory assessments conducted by DB^{+} and JL^{+}
Data analysis: JCG in consultation with CF
Writing: JCG and JW

Chapter 3 Non-verbal auditory object processing in dementia: study 2
Experimental design: JCG, JW, SC
Construction of tests, including automation in MATLAB: JCG
Data collection: JCG; some neuropsychological data collected by JH, ML and AB
Data analysis: JCG in consultation with LK
Writing: JCG and JW

Chapter 4 Distinct patterns of non-verbal auditory cognitive impairment in two cases of primary progressive aphasia
Experimental design: JCG, JW, SC
Construction of tests, including automation in MATLAB: JCG
Data collection: JCG; auditory assessments conducted by DB^{+} and JL^{+}
Data analysis: JCG in consultation with LK
Writing: JCG and JW

Chapter 5 Altered brain mechanisms of non-verbal sound analysis in Semantic dementia
Experimental design: JCG, JW, SC
Construction of fMRI paradigm, including automation in MATLAB: JCG
Data collection: JCG and JW, with technical support from JG*, SL*, and KJ*
Data analysis: JCG in consultation with GR
Writing: JCG and JW

Chapter 6 Impairments of auditory scene analysis in Alzheimer's disease
Experimental design: JCG, JW, SC
Construction of tests, including automation in MATLAB: JCG
Data collection: JCG; some neuropsychological data collected by JH, ML and AB
Data analysis: JCG in consultation with LK
Writing: JCG and JW

Unless otherwise indicated, all individuals involved in work are employees or students at the Dementia Research Centre, Institute of Neurology, University College London.

KEY: $^{+}$, affiliated to The Ear Institute, University College London; *, affiliated to the Functional Imaging Laboratory, Institute of Neurology, University College London; AB, **Aisling Buckley**, CF, **Chris Frost**; DB^{+}, **Doris-Eva Bamiou**; JCG, **Johanna C Goll**; JG*, **Janice Glensman**; JH, **Julia C Hailstone**; JL^{+}, **Jenny Lee**; JW, **Jason D Warren**; KJ*, **Kristian Johannesson**; LK, **Lois G Kim**; ML, **Manja Lehmann**; SC, **Sebastian J Crutch**; SL*, **Sheila Lee**.

8.5 Journal articles resulting from this work

8.5.1 Published journal articles

Goll, J.C., Crutch, S.J., Loo, J.H., Rohrer, J.D., Frost, C., Bamiou, D.E., Warren, J.D., 2010a. Non-verbal sound processing in the primary progressive aphasias. Brain. 133, 272-285.

Goll, J.C., Crutch, S.J., Warren, J.D., 2010b. Central auditory disorders: toward a neuropsychology of auditory objects. Curr Opin Neurol. 23(6), 617-27.

Goll J.C., Kim L.G., Hailstone J.C., Lehmann M., Buckley A., Crutch S.J., Warren, J.D., 2011. Auditory object cognition in dementia. Neuropsychologia. 49, 2755-65.

Goll J.C., Kim L.G., Ridgway, G. R., Hailstone J.C., Lehmann M., Buckley A., Crutch S.J., Warren, J.D., 2011. Impairments of auditory scene analysis in Alzheimer's disease. Brain (in press).

8.5.2 Submitted journal articles

Goll J.C., Crutch S.J., Warren, J.D., *submitted*. Distinct patterns of non-verbal auditory cognitive impairment in two cases of primary progressive aphasia.

Goll J.C., Ridgway, Crutch S.J., Theunissen, F.E., Warren, J.D., *submitted*. Nonverbal sound processing in semantic dementia: a functional MRI study.
.

doi:10.1093/brain/awp235 Brain 2010: 133; 272–285 | 272

BRAIN
A JOURNAL OF NEUROLOGY

Non-verbal sound processing in the primary progressive aphasias

Johanna C. Goll,[1] Sebastian J. Crutch,[1] Jenny H. Y. Loo,[2,3] Jonathan D. Rohrer,[1] Chris Frost,[1,4] Doris-Eva Bamiou[2,3] and Jason D. Warren[1]

1 Dementia Research Centre, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK
2 Department of Neuro-otology, National Hospital for Neurology and Neurosurgery, London, UK
3 Ear Institute, School of Life and Medical Sciences, University College London, UK
4 Medical Statistics Unit, London School of Hygiene and Tropical Medicine, University College London, UK

Correspondence to: Dr J. D. Warren,
Dementia Research Centre,
Institute of Neurology,
University College London,
Queen Square,
London WC1N 3BG,
UK
E-mail: jwarren@drc.ion.ucl.ac.uk

Little is known about the processing of non-verbal sounds in the primary progressive aphasias. Here, we investigated the processing of complex non-verbal sounds in detail, in a consecutive series of 20 patients with primary progressive aphasia [12 with progressive non-fluent aphasia; eight with semantic dementia]. We designed a novel experimental neuropsychological battery to probe complex sound processing at early perceptual, apperceptive and semantic levels, using within-modality response procedures that minimized other cognitive demands and matching tests in the visual modality. Patients with primary progressive aphasia had deficits of non-verbal sound analysis compared with healthy age-matched individuals. Deficits of auditory early perceptual analysis were more common in progressive non-fluent aphasia, deficits of apperceptive processing occurred in both progressive non-fluent aphasia and semantic dementia, and deficits of semantic processing also occurred in both syndromes, but were relatively modality specific in progressive non-fluent aphasia and part of a more severe generic semantic deficit in semantic dementia. Patients with progressive non-fluent aphasia were more likely to show severe auditory than visual deficits as compared to patients with semantic dementia. These findings argue for the existence of core disorders of complex non-verbal sound perception and recognition in primary progressive aphasia and specific disorders at perceptual and semantic levels of cortical auditory processing in progressive non-fluent aphasia and semantic dementia, respectively.

Keywords: auditory perception; non-verbal sound; agnosia; dementia; environmental sounds

Abbreviations: CI = confidence interval; FA = frequency average; HFA = high frequency average; MMSE = Mini-Mental State Examination; PNFA = progressive non-fluent aphasia; PPA = primary progressive aphasias; PTA = pure tone audiometry

Introduction

Since the key descriptions of Mesulam (1982) and Warrington (1975) the primary progressive aphasias (PPA) have attracted substantial clinical and neurobiological interest. These disorders together constitute a paradigm for understanding the neurodegenerative pathologies that produce discrete neuropsychological syndromes associated with focal cortical atrophy. Within the

Received May 5, 2009. Revised July 14, 2009. Accepted August 10, 2009. Advance Access publication October 1, 2009

frontotemporal lobar degeneration spectrum, two canonical PPA syndromes are recognized: progressive non-fluent aphasia (PNFA), associated with speech production breakdown and agrammatism, and atrophy predominantly affecting left inferior frontal and peri-Sylvian cortex (Mesulam, 1982; Nestor *et al*., 2003; Rohrer *et al*., 2008*a*, 2009); and semantic dementia, associated with impaired single word comprehension and additional non-verbal semantic deficits, and atrophy predominantly affecting the anterior temporal lobes with a left-sided emphasis (Warrington, 1975; Lambon Ralph *et al*., 2001; Hodges and Patterson, 2007; Rohrer *et al*., 2008*a*, *b*, 2009). The study of these disorders has focused on language deficits; however, spoken language (speech) is a highly specialized signal in acoustic, cognitive and evolutionary terms, representing a particularly significant species of complex sound (Griffiths *et al*., 1999). An accumulating body of convergent evidence suggests that disorders in the PPA spectrum are clinically, neuroanatomically and pathologically distinct, and further, that PNFA and semantic dementia are likely to have fundamentally different pathophysiological mechanisms (Nestor *et al*., 2003; Gorno-Tempini *et al*., 2004; Hodges and Patterson, 2007; Rohrer *et al*., 2008*a*). An important issue concerns the true language specificity of disorders in the PPA spectrum. These disorders might represent more general derangements of cortical signal processing and in particular, generic disorders of complex sound processing arising from more fundamental pathophysiological mechanisms in different PPA subtypes. However, the processing of non-verbal sounds has not been assessed systematically in PNFA or semantic dementia. There are clinical and neuroanatomical grounds to anticipate that PNFA and semantic dementia should lead to distinct deficits in the analysis and understanding of complex non-verbal sounds, and that these disorders of complex sound processing may provide insights complementary to the study of language processing in these disorders.

Clinically, patients with PNFA often report altered perception of sound, and non-verbal perceptual and expressive deficits sometimes dominate the clinical presentation (Confavreux *et al*., 1992; Otsuki *et al*., 1998; Uttner *et al*., 2006; Iizuka *et al*., 2007; Jörgens *et al*., 2008). Failure to correctly identify and respond to environmental noises not uncommonly accompanies semantic dementia, and a deficit in recognition of meaningful environmental sounds has been documented (Bozeat *et al*., 2000). Impaired recognition of familiar voices often accompanies the development of prosopagnosia as evidence of a more general defect of person knowledge in semantic dementia (Gainotti *et al*., 2003). Anatomically, the brunt of the pathological process in these diseases (Mesulam, 2003) generally falls on cortical regions that overlap with non-primary and association auditory cortical areas implicated in aspects of complex sound processing both in functional brain imaging studies in healthy subjects (Griffiths and Warren, 2002; Warren *et al*., 2005*b*) and in patients with focal brain lesions (Griffiths *et al*., 1999). More specifically, distinct neuroanatomical profiles, potentially relevant to the development of specific disorders of complex sound analysis, are associated with PPA: in PNFA, damage variably involves widespread peri-Sylvian areas (Nestor *et al*., 2003; Gorno-Tempini *et al*., 2004; Rohrer *et al*., 2008*a*, 2009), while in semantic dementia, damage is more stereotyped and typically anterior and inferior (predominantly left-sided) temporal lobe areas are most strikingly affected (Hodges and Patterson, 2007; Rohrer *et al*., 2008*b*, 2009).

By analogy with other categories of sensory information, the cortical processing of complex sounds is likely to be broadly hierarchically organized with more or less distinct stages of early perceptual analysis, representation of the structural features of auditory objects (apperceptive level) and attribution of meaning to those objects (semantic level) (Griffiths and Warren, 2002, 2004; Warren *et al*., 2005*b*) However, several issues complicate the assessment of complex sound processing in patients with cognitive impairment (Griffiths *et al*., 1999). In contrast to the visual agnosias, analogous disorders of complex sound processing have proved relatively difficult to define and clinically relevant models of auditory processing are needed. Furthermore, established neuropsychological instruments and normative data to assess these disorders systematically are lacking. The available clinical evidence has mainly been obtained either for visual without parallel auditory assessments, or via cross-modal response procedures (Bozeat *et al*., 2000; Garrard and Carroll, 2006, Crutch and Warrington, 2008). Within the auditory modality, instruments to specifically assess different levels of processing and potentially relevant interactions between processing stages (Clarke *et al*., 1996; Rogers *et al*., 2004; Kveraga *et al*., 2007) have not been widely applied. Finally, neuropsychological tests that rely on sustained attention, naming or other cross-modal response procedures may be contaminated by other cognitive deficits, making interpretation of any primary complex sound deficit more difficult.

Here, we set out to assess the processing of complex non-verbal sounds in detail, in a consecutive series of patients with the canonical PNFA and semantic dementia subtypes of PPA. We designed a novel experimental neuropsychological battery to probe complex sound processing at perceptual, apperceptive and semantic levels of processing, using within-modality response procedures that minimized other cognitive (in particular, linguistic) demands. In order to assess the modality specificity of any auditory disorder identified, we designed matching tests in the visual modality. Our hypotheses were three-fold: that complex sound processing is disordered in PPA; that specific disorders of complex sound processing accompany and distinguish the PNFA and semantic dementia subtypes of PPA; and that the characteristics of the cortical auditory syndromes reflect the core pathophysiological processes underpinning these PPA subtypes.

Methods

Subjects

Twenty consecutive patients (12 males) who met current consensus criteria (Neary *et al*., 1998) for a diagnosis of PNFA ($n = 12$) or semantic dementia ($n = 8$) were recruited from a tertiary cognitive disorders clinic. Twelve healthy control subjects with no history of neurological or psychiatric illness also participated. Demographic data for all subjects are summarized in Table 1. Patient and control groups were well-matched for educational background, and the patient groups were well-matched for disease duration. Males were

Table 1 General demographic data for all subjects

	N		Age (years)	Education (years)	Disease duration (years)
	Total	Female	Mean (SD)	Mean (SD)	Mean (SD)
PNFA	12	4	73.1 (6.1)	13.4 (2.6)	6.4 (2.5)
Semantic dementia	8	4	61.5 (4.9)	13.1 (2.3)	6.3 (1.4)
Control	12	8	71.3 (4.9)	12.0 (2.3)	N/A

SD = standard deviation

under-represented in the control group relative to the patient sample. The mean age of the patients with semantic dementia was younger (Mann–Whitney $P < 0.01$) than either the PNFA group or the healthy control group. Age and gender were accordingly incorporated as covariates in all subsequent analyses.

Brain image acquisition

Brain MRI scans were acquired in all subjects on a 1.5 T GE Signa scanner (General Electric, Milwaukee, WI). T_1-weighted volumetric images were obtained using a spoiled fast gradient recalled acquisition in steady state (GRASS) sequence technique with a 24 cm field of view and 256×256 matrix to provide 124 contiguous 1.5 mm thick slices in the coronal plane. The scan acquisition parameters were as follows: repetition time = 15 ms; echo time = 5.4 ms; flip angle = 15°; inversion time = 650 ms.

Assessment of subcortical auditory function

In the majority of patients (14/20), peripheral hearing was assessed using pure tone audiometry (PTA), tympanometry and transient otoacoustic emissions. In the remaining patients and all healthy control subjects a brief PTA screening assessment was used. Auditory brainstem responses were also recorded in a subset of patients (10/20). These procedures are summarized in Appendix A, available as supplementary material online. For each subject, pure tone thresholds at 0.5, 1 and 2 KHz at each ear were averaged to give a '3 Frequency Average' (3FA), and thresholds at 4, 6 and 8 KHz were averaged to give a 'High Frequency Average' (HFA). 3FA and HFA were then compared with age-corrected norms (Davis, 1995) and categorized as normal or abnormal. Lastly, for each subject, categorizations were collapsed across ears to give a single measure for each subject within each hearing range (3FA-S, HFA-S), which was considered abnormal only if both ears were abnormal.

General neuropsychological assessment

General neuropsychological functions were assessed in patients using standard measures (summarized in Table 2), at the time of initial ascertainment and contemporaneous with the experimental assessment. Baseline tests provided a neuropsychological characterization of PPA subgroups: these included measures of non-verbal fluid intelligence and executive processing (Raven's matrices: Raven *et al*., 2003; Trail Making: Reitan, 1959), attention (Dual Number Cancellation: Mohs *et al*., 1997), object naming (novel test), spoken word repetition (McCarthy and Warrington, 1984), word comprehension (a shortened 30 item version of the British Picture Vocabulary Scale, Dunn *et al*., 1982), grammar processing (a shortened 20 item version of the Test of Reception of Grammar: Bishop, 1989), reading (novel test of irregular words) and face recognition (Warrington and James, 1967). Contemporaneous tests allowed correlation of general neuropsychological functions with experimental findings: these tests comprised measures of executive function (Non-Verbal Design Fluency, Delis *et al*., 2001) verbal semantic processing (Synonyms test, Warrington *et al*., 1998), visual (pictorial) recognition memory (the Camden Memory Tests, Warrington, 1996) and visual apperceptive processing (the Object Decision test, Warrington and James, 1991). All patients completed the Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975), a general cognitive screening instrument, as an index of disease severity at the time of the experimental assessment.

Experimental assessment of auditory cognition

General testing procedure

All experimental neuropsychological tests were run under Matlab 7.3® (www.mathworks.com) on a notebook computer. Subject responses were entered directly by the experimenter and saved for offline analysis. Sounds were delivered using a high-fidelity external soundcard (Edirol® UA-4FX) and linear headphones (Sennheiser® HD265) at comfortable listening level (peak absolute sound pressure levels between 70 and 100 dB). Images were presented on a 17 in. high-resolution monitor. For all tests, performance on each test item was probed using a simple question with two alternative responses. Answers could be given verbally, or in the case of speech output difficulty, by pointing to a prompt sheet displaying the two responses. Each test was prefaced with a brief example phase to ensure that the subject understood the test.

Early perceptual level

This test was designed to assess early perceptual processing of auditory stimuli beyond the level of elementary sensory encoding in the auditory periphery, based on the discrimination of complex sound properties. Most natural sounds contain energy distributed across multiple frequencies with variable energy (intensity). This patterning of frequency and intensity is the 'spectral shape' of the sound (Warren *et al*., 2005*a*) and is presented schematically in Fig. 1A. Spectral shape is one important determinant of timbre, a key factor in the perception of sound identity. Since spectral shape perception necessitates the integration of intensity information across multiple frequency bands, it is operationally analogous to shape perception in vision, which requires the integration of information across two (spatial) dimensions. Here, we designed tests to manipulate shape information in auditory and visual objects, respectively.

Stimuli

Sounds were digitally generated using a Matlab-based signal-synthesis algorithm (Warren *et al*., 2005*a*) enabling generation of harmonic

Table 2 Results of general neuropsychological assessment: raw scores and differences in group means adjusted for age and gender

	Raw scores Mean (SD)				Differences in group means Mean difference (95% CI)		
	Max score	PNFA (*N* = 12)	Semantic dementia (*N* = 8, *N* = 7)	Control (*N* = 40)	PNFA–semantic dementia	PNFA–Control	Semantic dementia–control
Baseline Neuropsychology							
Non-verbal intelligence (shortened Raven's matrices)	12	5.2 (2.8)	*8.1 (2.7)	7.4 (2.7)	−1.6 (−4.5 to 1.5)	−1.8 (−3.7 to 0.1)	−0.2 (−2.6 to 2.0)
Naming	20	13.8 (5.7)	*4.1 (3.8)	19.4 (1.1)	**10.4 (5.7 to 14.0)**	**−5.2 (−8.7 to −2.7)**	**−15.7 (−18.1 to −12.2)**
Word-picture matching (shortened BPVS)	20	19.3 (1.2)	*12.1 (5.4)	19.9 (0.3)	**7.4 (3.7 to 11.2)**	−0.4 (−1.5 to 0.1)	**−7.8 (−11.7 to −4.2)**
Famous face recognition	12	10.5 (2.2)	*6.4 (5.3)	11.6 (0.7)	**3.8 (0.3 to 7.9)**	**−1.2 (−2.7 to −0.1)**	**−5.0 (−8.9 to −1.6)**
Famous face recall	12	5.9 (3.6)	*1.0 (2.2)	9.6 (1.6)	**4.4 (1.1 to 6.8)**	**−3.9 (−6.2 to −1.9)**	**−8.3 (−9.6 to −5.7)**
Repetition	30	24.5 (9.3)	*30.0 (0.0)	29.9 (0.3)	**−5.1 (−12.1 to −1.4)**	**−5.2 (−11.5 to −1.4)**	−0.1 (−1.6 to 1.3)
Reading	30	19.5 (8.1)	*14.9 (10.7)	27.0 (2.9)	5.0 (−4.5 to 14.1)	**−7.3 (−12.8 to −3.2)**	**−12.4 (−20.2 to −4.7)**
Grammar (shortened TROG)	20	16.1 (2.6)	*15.6 (3.6)	19.4 (0.7)	0.6 (−2.3 to 4.1)	**−3.3 (−4.9 to −1.8)**	**−3.9 (−6.9 to −1.7)**
Dual number cancellation	40	13.4 (5.0)	*22.7 (5.9)	24.9 (5.3)	**−5.7 (−11.0 to −0.7)**	**−10.1 (−13.1 to −6.5)**	−4.4 (−8.9 to 0.2)
Trails Making—condition A (scaled)	–	4.9 (3.4)	*8.4 (3.2)	9.3 (2.2)	**−3.5 (−6.3 to −0.4)**	**−4.3 (−6.1 to −2.1)**	−0.8 (−3.2 to 1.5)
Trails Making—condition B (scaled)	–	4.6 (2.9)	*9.0 (3.4)	10.2 (2.7)	**−4.4 (−7.6 to −1.8)**	**−5.6 (−7.5 to −3.8)**	−1.2 (−3.3 to 1.7)
Contemporaneous Neuropsychology							
MMSE	30	20.9 (6.6)	18.9 (6.8)		−0.6 (−9.9 to 10.5)		
Object decision	20	17.1 (6.1)	16.5 (3.1)	17.3 (2.5)	0.8 (−1.4 to 3.4)	−0.3 (−1.2 to 0.7)	−1.1 (−3.7 to 1.0)
NVDF (sum of scaled scores)	–	6.4 (1.8)	8.6 (2.5)	12.4 (2.4)	**−2.2 (−4.2 to −0.2)**	**−5.9 (−7.2 to −4.7)**	**−3.7 (−5.4 to −2.0)**
Recognition memory (pictorial)	30	27.4 (3.3)	24.8 (7.4)	29.6 (0.7)	3.1 (−1.1 to 9.4)	**−2.0 (−4.2 to −0.7)**	**−5.1 (−11.6 to −1.1)**
Synonyms—concrete (2nd error)	25	10.8 (6.1)	3.9 (3.6)	21.5 (5.3)	**8.7 (4.1 to 13.0)**	**−10.1 (−13.5 to −5.6)**	**−18.8 (−21.2 to −15.2)**
Synonyms—abstract (2nd error)	25	9.3 (6.3)	4.4 (7.4)	22.1 (4.8)	4.9 (−3.0 to 10.1)	**−13.1 (−16.1 to −9.2)**	**−18.0 (−22.2 to −11.0)**

Significant differences between groups are in bold. Controls comprised a previous age- and gender-matched sample.
BPVS = British Picture Vocabulary Scale; NVDF = Non-Verbal Design Fluency; TROG = Test of Reception of Grammar. CI = confidence interval.

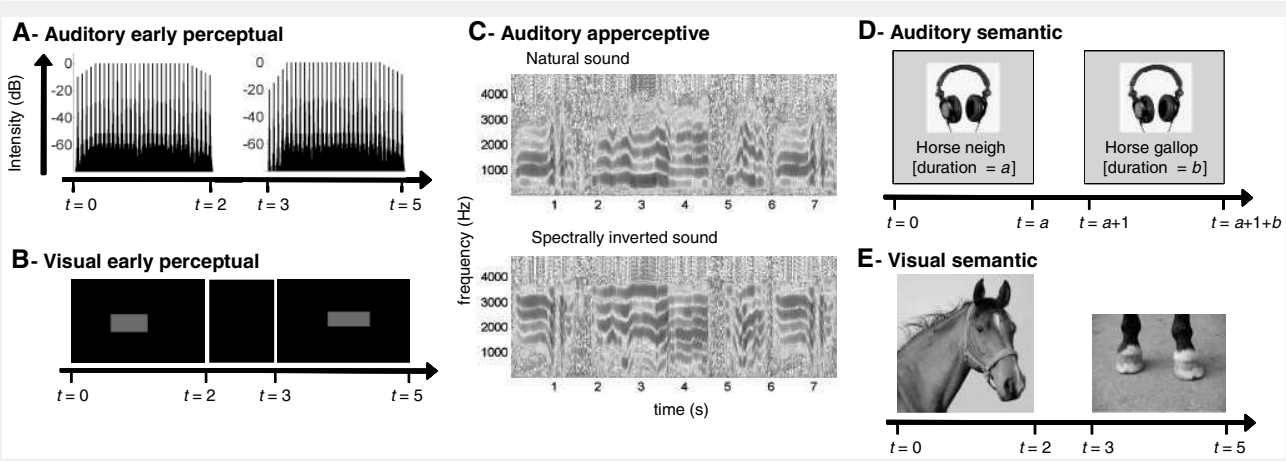


Figure 1 Schematic of experimental stimuli and presentation sequences (**A** and **B**). Schematics of auditory and visual early perceptual stimuli, and the presentation sequence used. (**C**) Schematic of spectral inversion of a complex sound, as used in the auditory apperceptive test. (**D** and **E**) Examples of auditory and visual semantic stimulus pairs, and a schematic of the presentation sequence used. t = time (s).

series with specified spectral shape. Different 'trapezoidal' spectral shapes were created in the frequency domain by varying the gradient of the 'ascending' slope of the frequency trapezoid (see Fig. 1A and example sound 1, available as supplementary material online). Frequency bandwidth, sound duration and temporal envelope were held constant. Fundamental frequency and average intensity (root mean square level) varied across the stimulus set, to reduce any tendency for subjects to use the absolute intensity level in a particular frequency band to perform the test. Thirty-two sound pairs were created: 16 'same' pairs comprising identical sounds, and 16 'different' pairs comprising sounds that differed only in spectral shape. Sounds in each pair were presented sequentially (inter-stimulus interval 1 s).

As visual analogues of the spectral shape stimuli, rectangles of varying dimensions were generated by holding total flux (area) constant, while varying the height/length ratio. Rectangles had constant hue and were presented on a uniform black background (Fig. 1B). Thirty-two rectangle pairs were created (16 same, 16 different). To minimize differences in working memory load between stimulus modalities, rectangles within each pair were presented sequentially with the same inter-stimulus interval as the sound pairs.

Task

Stimulus pairs were presented in a fixed balanced order: experimental conditions were evenly distributed in a non-predictable fashion throughout the test sequences. For each test, after presentation of each pair, the subject was asked 'Are they the same or different?'

Apperceptive level

This test was designed to assess the status of 'apperceptive' processing for complex sounds. The existence of an apperceptive level of object processing is well-established in vision, and corresponds to a post-sensory stage of perceptual categorization that generates (or accesses) structural representations: sets of distinctive geometric and volumetric features that enable object identity to be abstracted despite changing contexts and viewpoints. Deficits at this level produce 'apperceptive agnosia', in which patients characteristically have difficulty in identifying the objects presented from unusual (non-canonical) viewpoints or under degraded viewing conditions. While limited evidence suggests that apperceptive deficits also exist in the auditory modality (e.g. in music: Peretz *et al*., 1994), their generality remains uncertain. In order to assess the integrity of putative pre-semantic object representations for complex sounds, we devised a test requiring differentiation of real (possible) and novel (impossible) sounds that might be considered an auditory 'object decision' test, analogous to the object decision test in vision (Warrington and James, 1991). The key experimental manipulation here was spectral inversion (Blesser, 1972). The spectral inversion procedure flips the energetic frequencies present in a broadband sound (i.e. exchanges the energy present between higher and lower frequencies) about a user-specified frequency value (Fig. 1C) to create a frequency structure that is 'impossible' in a natural sound. Example stimuli are available online: sound 2a is a natural animal call and sound 2b is the same call after spectral inversion. This procedure retains the spectrotemporal complexity of a natural sound but produces a percept of an artificial or 'alien' sound in normal listeners (Scott *et al*., 2000). While spectral inversion animal calls (for example) sound highly artificial, the procedure preserves many acoustic features of the original sound, such that spectral inversion and natural sounds are not differentiated by spectral content or temporal envelope alone. Rather, spectral inversion alters more complex acoustic features, including spectral and joint spectrotemporal modulations that are likely to be critical for disambiguating natural from synthetic sounds (e.g. Chi *et al*., 2005). We also wished to investigate whether this process of auditory object representation might be modulated by the relative ease or difficulty with which individual stimuli are identified (the procedure used to quantify sound identifiability is described in Appendix B, available as supplementary material online).

Stimuli

Twenty animal and human vocalizations were selected from online sound databases (e.g. www.sonomic.com; www.soundrangers.co.uk). Individual items were chosen to vary in the ease with which they are identified by normal subjects: this effect was quantified in a second group of healthy age-matched controls who did not participate in the experiment proper [n = 18, 17 females; age: mean = 68.7 years [standard deviation (SD) = 6.7]; National Adult Reading Test IQ: mean = 122.6 (SD = 4.5)]. For each item, subjects were asked (i) 'What is it?' and (ii) 'How difficult was that to recognize?'

(subjects answered using a 6-point Likert scale: 0 = did not recognize; 1 = very difficult; 2 = difficult; 3 = moderate; 4 = easy; 5 = very easy). Across the set of sounds, subject responses to (i) provided an index of frequency of correct identification while (ii) provided a rating of difficulty of identification for each sound. Further details about this procedure, the complete stimulus list and their corresponding ratings are presented in Appendix B, available as supplementary material online. For the experimental test, each natural sound was modified using a method of spectral inversion to create an additional set of 20 novel sounds.

As a visual analogue of this novel auditory apperceptive test, patients completed an established and normed test of visual apperception (Object Decision, Warrington and James, 1991) based on the discrimination of real from novel 2D silhouettes. The test comprises 20 arrays of four silhouettes.

Task

For the auditory apperceptive test, the 40 sounds (20 non-spectral inversion, 20 spectral inversion) were presented individually in a fixed balanced order: conditions were randomly distributed throughout the test sequence. For each sound, the subject was asked: 'Is it a real thing or not a real thing?' The visual apperceptive test was administered in standard fashion (Warrington and James, 1991): on each trial, the subject was shown the four silhouettes in an array, and asked to point to the real object.

Semantic level

This test was designed to assess the association of conceptual meaning with complex sounds (semantic level processing). The status of 'associative agnosia' is less well-established in the auditory than the visual modality (e.g. De Renzi *et al*., 1969; Taylor and Warrington, 1971; Anaki *et al*., 2007), particularly in the context of degenerative disease (e.g. Bozeat *et al*., 2000; Garrard and Carroll, 2006). Here, we used a within-modality test to assess semantic processing of sounds and their visual analogues.

Stimuli

Environmental sounds were obtained from online sound databases (e.g. www.sonomic.com; www.soundrangers.co.uk). Thirty-two individual sounds representing a range of human and animal sounds and environmental noises were chosen and arranged to constitute 32 pairs of sequentially presented sounds (see Table B2, Appendix B, available as supplementary material online). Picture analogues of the sound pairs were obtained using online image search engines and image databases (e.g. http://images.google.co.uk, www.flckr.co.uk). Pictures were 32 visual object parts, chosen such that each object part was easily recognizable as a distinct entity in isolation from the rest of the larger object to which it belongs. The identifiability of the sounds and pictures was assessed using the same procedure as for the stimuli used in the apperceptive test (Appendix B, available as supplementary material online) in the same group of untrained healthy age-matched controls. Both auditory and visual semantic stimuli were highly recognizable: identifiability ratings showed that although pictures were overall easier to identify than sounds, sounds were nonetheless frequently identified successfully, and moreover, stimulus identification difficulty ratings were similar between the two modalities.

In the experimental test, sounds were paired such that the individual sounds in a pair had dissimilar acoustic characteristics, to reduce the availability of perceptual matching cues. In 16 'same' pairs, sounds were produced by the same source (e.g. horse neighing, horse galloping; example sound 3, available as supplementary material online). In 16 'different' pairs, sounds were produced by different sources (e.g. horse neighing, human coughing). The test design is presented schematically in Fig. 1D. All 32 sounds appeared once in the 'same' and once in the 'different' condition, to control for item-specific effects. From the set of 32 pictures, 16 'same' and 16 'different' pairs were created such that pictures within a pair had dissimilar visual perceptual characteristics (Fig. 1E). All 32 pictures appeared once in the 'same' and once in the 'different' condition. To minimize differences in working memory load between stimulus modalities, pictures within each pair were presented sequentially with the same inter-stimulus interval as the sound pairs. All sound and picture pairs, together with their normative data, are listed in Table B2 in Appendix B (available as supplementary material online).

Task

Stimulus pairs were presented in a fixed balanced order: conditions were randomly presented throughout the test sequence. To reduce any effects from semantic priming between modalities, subjects completed the semantic picture test first, followed by at least one other unrelated test and then the semantic sound test. On each sound trial, the subject was asked: 'Are the sounds made by the same thing or different things?' On each picture trial the subject was asked: 'Are the pictures part of the same thing or different things?'

Analysis of behavioural data

Group data

Linear regression models were used to relate scores for each test (general neuropsychological and experimental) to group membership (PNFA, semantic dementia or healthy control). Each model included age and gender as covariates, with the exception of the models for non-verbal design fluency and trail making since these are internally corrected for age and gender. Since normality assumptions were not satisfied, bootstrap confidence intervals (95% CIs, bias-corrected, accelerated with 2000 replications) are reported and used to infer statistical significance. The subset of 'real' (non-spectral inversion) sounds in the auditory apperceptive test was submitted to a further analysis: a mixed effects logistic regression model was used to relate, for each sound, the probability of a correct response to its corresponding difficulty rating (quantified using the procedure described in Appendix B). The model included fixed effects (sound difficulty rating, group membership and their interaction) and crossed random effects (individual subjects, individual sounds). The model was fitted using a Laplacian approximation. All analyses were carried out using Stata 10^{TM}.

In order to assess factors influencing performance on particular components of the experimental auditory battery, patient performance on individual auditory tests was assessed in relation to other tests in the battery, general neuropsychological functions and general measures of disease severity (clinical disease duration, MMSE) using a correlation analysis (Spearman's ρ). This analysis was carried out separately in the PNFA and semantic dementia groups, to take into account the different auditory profiles of each PPA subgroup.

Individual data: Auditory and visual cost analyses

Individual subject performance profiles were examined for modality specific effects. For both the perceptual and semantic levels of assessment, individual subjects were categorized according to whether their performance showed an 'auditory cost' (performance worse on the auditory than the analogous visual test) or no auditory cost (performance equivalent between modalities or worse in the visual modality). Subjects were also categorized according to whether

thei performance showed a 'visual cost' at each test level using analogous criteria. Proportions of subjects showing costs were compared between groups using exact logistic regression adjusting for age and gender.

Results

Brain imaging findings

Individual brain magnetic resonance findings for patients in the PNFA and semantic dementia groups are presented in Fig. 2. Inspection of sections aligned to show key auditory cortical areas in and surrounding the superior temporal plane gives an impression of the range of variation in the distribution and severity of structural damage involving these areas in PNFA and semantic dementia. In PNFA, atrophy showed wide variation both in the degree of leftward cerebral asymmetry and, within each hemisphere, the relative involvement of anterior and posterior areas. In contrast, the semantic dementia group showed a more uniform atrophy pattern with involvement chiefly of the anterior temporal lobes, initially with predominant involvement of the left temporal lobe and increasingly bitemporal involvement with increasing disease duration.

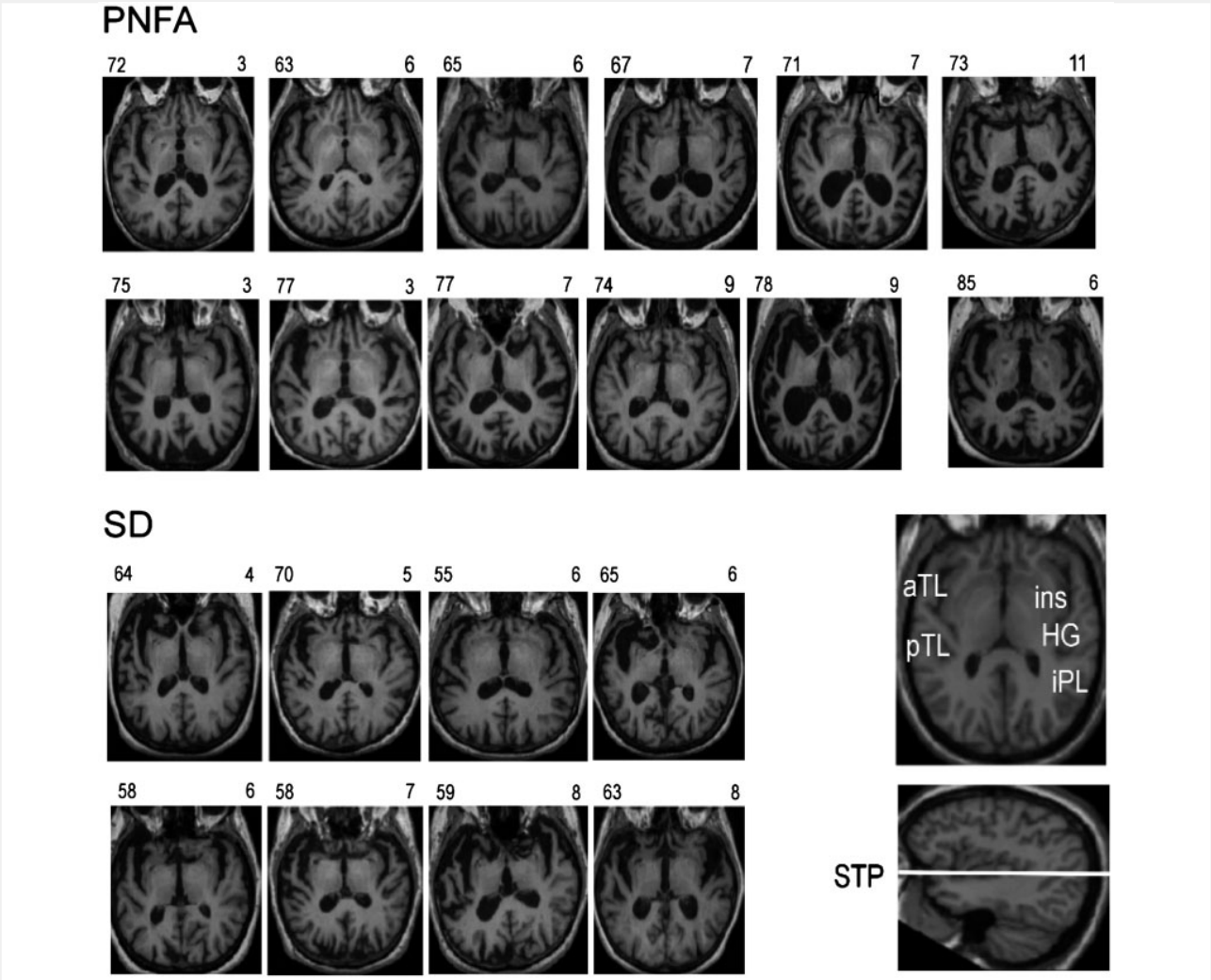


Figure 2 MRI brain sections showing auditory cortices in PNFA and semantic dementia (SD) patients. Sections of each patient's volumetric T_1-weighted magnetic resonance brain volume are shown. Sections have been tilted to run along the superior temporal plane (STP) to show key auditory cortical areas: the site of primary auditory cortex in Heschl's gyrus (HG), and surrounding non-primary areas in anterior temporal lobe (aTL), posterior superior temporal gyrus and planum temporale (posterior temporal lobe: pTL), insula (ins) and inferior parietal lobe (iPL). For all brain images, the left hemisphere is shown on the left. For reference normal auditory cortical anatomy is shown on the inset sections (lower right) from the brain of a healthy younger individual. Brain images from the PNFA group are shown above and the semantic dementia group below. Above each image is shown the patient's age (left) and clinical disease duration (right) in years at the time of the scan. Within each group brain images have been arranged loosely in order of disease duration; the PNFA group had an older age range and a wider variation in age, and to reflect this, images have been further clustered to show younger patients above and older patients below.

Subcortical auditory function

Abnormal PTA profiles were documented in 2/12 patients in the PNFA group (both 3FA; bilateral), 2/8 patients in the semantic dementia group (one 3FA, one HFA; bilateral), and one healthy control subject (HFA; bilateral). Otoacoustic emissions were consistent with PTA thresholds for all individuals. Abnormal auditory brain-stem responses were recorded in 4/6 patients (two bilateral) in the PNFA group and 2/4 patients (none bilateral) in the semantic dementia group. PTA and auditory brain-stem response data are summarized in Table A1 (Appendix A, online supplementary material).

General neuropsychological assessment

On baseline assessment of general neuropsychological functions, the PNFA and semantic dementia groups had profiles consistent with their clinical diagnoses (Table 2): the PNFA group showed impairments chiefly affecting naming, single word repetition, reading, executive function and attention, while the semantic dementia group showed more severe impairment of naming with additional deficits of single word comprehension and face recognition but normal single word repetition and executive functions. On contemporaneous general neuropsychological assessment, both groups showed normal performance in the visual object decision task but impaired performance on other measures relative to healthy controls (Table 2). The PNFA group performed significantly less well than the semantic dementia group on non-verbal design fluency, while the semantic dementia group performed significantly less well than the PNFA group on the concrete words component of the synonyms test.

Experimental assessment of auditory cognition

Raw behavioural data are shown in Fig. 3. Bootstrap analyses as described in the Methods section were used to determine the significance of group differences and are presented in Table 3. The overall patterns of disease group performance across the set of experimental tests are summarized in Table 4.

Early perceptual level

On the auditory early perceptual test, the PNFA group was significantly more impaired than both the healthy control group and the semantic dementia group. The performance of the semantic dementia group did not differ significantly from controls. Performance on the test did not differ materially for patients with and without peripheral hearing loss. On the analogous early visual perception test, performance was equivalent between disease groups and did not differ significantly from controls.

Apperceptive level

On the auditory apperceptive test, both the PNFA group and the semantic dementia group were impaired, relative to healthy controls. The performance of the PNFA group did not differ significantly overall from the semantic dementia group. However, inspection of individual data (Fig. 3) suggests that there may be a subgroup of patients with PNFA with more marked impairment on this test.

The performance patterns across the three groups were further assessed for any effect of recognition difficulty (identifiability) within the subset of 'real' (non-spectral inversion) sounds. Sound identifiability was significantly associated with performance in the healthy control group: a one unit reduction in the recognition difficulty of a sound (Appendix B, available as supplementary material online) was associated with a 110% increase in the odds of correctly stating that the sound was real (95% CI: 6–316%, $P = 0.03$). A similar magnitude of association was seen in the PNFA group [75% odds increase per unit difficulty reduction (95% CI: 8–183%, $P = 0.02$)], but not in the semantic dementia group [9% odds increase per unit difficulty reduction (95% CI: –52–144%, $P = 0.8$)]. Despite the variation in the significance of this association across the three groups (significant in the control and PNFA groups; non-significant in the semantic dementia group), a global test for a difference in the association among groups was not statistically significant, reflecting the wide CIs within each group.

On the standardized visual apperceptive (Object Decision) test, regression analysis did not show significant differences in mean performance between the disease groups. One of the 12 patients with PNFA and 1 of the 8 patients with semantic dementia scored below the 5th percentile of published age control norms (Warrington and James, 1991). Although this visual test and the experimental auditory apperceptive test were not directly comparable, it is noteworthy that on the corresponding auditory test 7/12 patients with PNFA and 5/8 patients with semantic dementia scored below the range of the healthy control sample. These findings would be in keeping with a more severe impairment of apperceptive processing within the auditory than the visual modality.

Semantic level

On the auditory semantic test, the PNFA and the semantic dementia groups were comparably impaired relative to healthy controls. The performance of the PNFA group did not differ significantly from the semantic dementia group. On the visual semantic test, both disease groups were impaired with respect to the control group; however, performance of the semantic dementia group was significantly worse than the PNFA group.

Correlation analyses

In the PNFA group, performance on both the auditory perceptual task and the auditory semantic task was positively associated (ρ 0.60; $P < 0.05$) with performance on the auditory apperceptive task. Performance on the auditory apperceptive task was also positively associated (ρ 0.70; $P < 0.05$) with performance on the visual object decision task. Experimental test performance was not significantly associated with other contemporaneous general neuropsychological or disease severity measures in the PNFA group. In the semantic dementia group (but not the PNFA group), performance on the auditory semantic task was strongly positively associated (ρ 0.97; $P < 0.001$) with performance on the visual semantic task, with some evidence of a positive association with

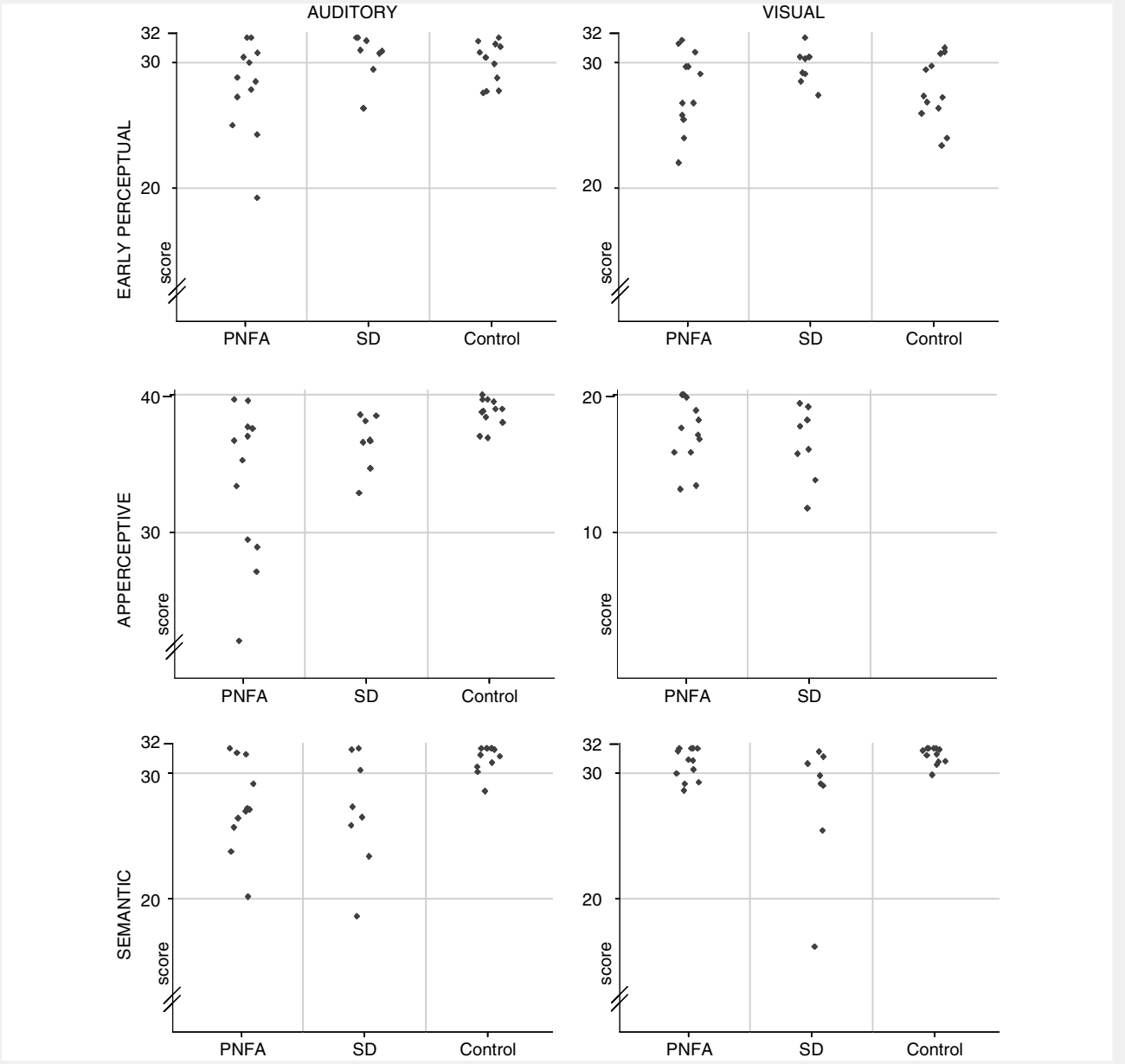


Figure 3 Performance on experimental subtests: raw data. SD = semantic dementia

performance on the Synonyms test (ρ 0.65; $P = 0.08$); performance on the auditory semantic task was also associated with general measures of disease severity (disease duration, ρ –0.97, $P < 0.001$; MMSE score, ρ 0.89, $P < 0.001$), but not with auditory apperceptive performance. In neither the PNFA nor the semantic dementia group was performance on any experimental auditory task significantly associated with a contemporaneous measure of executive function (non-verbal design fluency).

Individual data: auditory and visual cost

There was evidence ($P < 0.05$) that patients with PNFA were more likely than patients with semantic dementia to exhibit an auditory cost on the early perceptual test, but not on the semantic test (detailed results presented in Appendix C, Table C1, available as supplementary material online). Examining the individual data, on the early perceptual test, 7/12 patients with PNFA showed an auditory cost, compared with 1/8 patients with semantic dementia; and on the semantic test, 10/12 patients with PNFA showed an auditory cost, compared with 4/8 patients with semantic dementia. There was also borderline statistically significant evidence ($0.05 < P < 0.1$) that individuals with PNFA were less likely to exhibit a visual cost than each of the other groups.

Discussion

Here, we have defined specific disorders of complex non-verbal sound processing in canonical subtypes of PPA; PNFA and

Table 3 Experimental data: differences in group means adjusted for age and gender

	Auditory			Visual		
		95% Confidence Interval			95% Confidence Interval	
	Mean difference	Lower	Upper	Mean difference	Lower	Upper
Auditory early perceptual				Visual early perceptual		
PNFA–Semantic dementia	**−4.2**	**−9.1**	**−1.1**	−1.5	−5.4	1.7
PNFA–Control	**−3.4**	**−6.5**	**−1.4**	−0.1	−3.0	2.4
Semantic dementia–Control	0.8	−1.5	3.3	1.4	−1.0	3.9
Auditory apperceptive				Visual apperceptive[a]		
PNFA–Semantic dementia	−1.5	−5.2	1.8	0.9	−1.8	4.5
PNFA–Control	**−5.9**	**−9.7**	**−3.4**			
SD–Control	−4.4	−7.2	−2.0			
Auditory semantic				Visual semantic		
PNFA–Semantic dementia	0.9	−3.9	5.6	**3.0**	**0.3**	**8.9**
PNFA–Control	**−4.1**	**−6.5**	**−2.2**	**−1.4**	**−3.0**	**−0.5**
Semantic dementia–Control	**−5.0**	**−9.6**	**−1.2**	**−4.4**	**−11.1**	**−1.7**

Significant differences between groups are in bold.
a Although the visual apperceptive (Object Decision) test aimed to probe similar cognitive processes to the auditory apperceptive test, it is not precisely analogous: see text for details.

Table 4 Summary of disease group performance patterns on experimental tests

	Disease group			
	PNFA		Semantic dementia	
Cognitive processing level	Auditory modality	Visual modality	Auditory modality	Visual modality
Early perceptual	++	−	−	−
Apperceptive	+	−	+	−
Semantic	+	+	+	++

++ = significant deficit compared with alternate patient group and healthy controls;
+ = significant deficit compared with healthy controls; − = no significant deficit;

semantic dementia. Both the PNFA and semantic dementia patient groups had deficits of non-verbal sound analysis compared with healthy age-matched individuals. There was evidence for relative specificity of deficits in PNFA and semantic dementia: deficits of early auditory perceptual analysis were more common in PNFA; deficits of semantic processing occurred in both syndromes but were relatively modality specific in PNFA and part of a more severe generic semantic deficit in semantic dementia; while deficits of apperceptive processing occurred in both PNFA and semantic dementia, albeit with evidence that the mechanism of the deficit differed between the two syndromes. Patients with PNFA were more likely to show more severe auditory than visual deficits as compared to patients with semantic dementia. The experimental design here ensured that our findings were not attributable to the effect of certain potentially confounding factors, such as cross-modal or verbal-response procedures. While it is likely that the experimental tests engaged other cognitive operations (for example, non-verbal working memory and executive processing) in addition to complex sound processing *per se*, we did not find evidence in a correlation analysis that group-specific effects were attributable to such generic cognitive deficits; nor did these differences simply reflect subcortical auditory dysfunction or disease duration.

The auditory profiles of the PNFA and semantic dementia groups suggest likely cognitive mechanisms in these two PPA syndromes. The more severe impairments at earlier stages of perceptual processing of complex sounds in PNFA versus semantic dementia are consistent with a core perceptual defect in the cortical processing of complex sound information in PNFA. The additional deficits of apperceptive and semantic levels of processing exhibited by patients with PNFA would follow as a consequence of the primary perceptual defect, if complex sound information is processed serially along a hierarchically organized cortical pathway (Griffiths and Warren, 2004). The observation of correlated performance on perceptual, apperceptive and semantic tests in the PNFA group here offers some support for such an interpretation. However, this evidence does not rule out the possibility of additional non-verbal semantic impairment in PNFA (we note, for example, that patients with PNFA did not perform normally on a visual semantic matching test, even though they performed significantly better than patients with semantic dementia). Cortical processing of complex sound information need not be exclusively serial: indeed, interactions between different processing stages are likely on both theoretical and empirical grounds (Griffiths and Warren, 2004; Rogers *et al*., 2004; Kveraga *et al*., 2007). In contrast to the situation in

PNFA, auditory deficits exhibited by patients with semantic dementia were restricted to higher order processing stages and semantic deficits were more severe, with correlated involvement of the auditory and visual modalities: this is the pattern of deficits predicted to arise from a core defect of multimodal semantic knowledge, consistent with a growing body of neuropsychological work in semantic dementia (Bozeat *et al*., 2000; Lambon Ralph *et al*., 2001; Coccia *et al*., 2004; Hodges and Patterson, 2007; Rami *et al*., 2007).

The patterns of performance of the disease groups on the auditory apperceptive test may give further clues to the core cognitive deficits in each group: both groups were impaired; however the PNFA group, unlike the semantic dementia group, exhibited sensitivity to the identifiability of the stimuli, and auditory apperceptive performance was correlated with auditory semantic performance in the PNFA group but not the semantic dementia group. Further, in the PNFA group (but not the semantic dementia group), auditory apperceptive performance was correlated with visual apperceptive performance, raising the possibility that analogous cortical mechanisms might mediate object representation in each modality. Perceptual attributes of individual sounds are likely to have contributed substantially to the difficulty of identification factor that we have quantified here: cat calls, for example, have rather variable spectrotemporal characteristics despite belonging to a single, rather narrow, semantic field. We propose that loss of fidelity of perceptual representations affects categorization and ultimately recognition of complex sounds in PNFA, whereas sound recognition in semantic dementia is chiefly affected by a primary semantic level impairment. As the PNFA and semantic dementia groups were comparably impaired in their overall performance on the auditory apperceptive test, the processing of basic categorical information about the characteristics of natural sounds may depend both on perceptual and 'top down' semantic factors, as proposed in certain theoretical models of auditory object processing (Griffiths and Warren, 2004). Indeed, patients with semantic dementia have been shown to have deficits of visual object decision processes, and the relative dependence on semantic factors (e.g. processing of chimaeric versus nonsense objects) is likely to influence performance (Hovius *et al*., 2003). However, in line with previous experimental evidence from other modalities in semantic dementia, it may be that super-ordinate categorization of complex sounds can be achieved even where explicit identification is not possible (Hodges and Patterson, 2007; Crutch and Warrington, 2008). It is also possible that at least some patients with semantic dementia may develop a true apperceptive deficit for the representation of complex auditory objects, perhaps analogous to deficits of perceptual face analysis previously documented in some patients with progressive prosopagnosia and more posterior extension of the pathological process within the temporal lobe (Joubert *et al*., 2003). We do not argue for a simple dichotomy of perceptual and semantic auditory defects in PNFA versus semantic dementia: rather, it is likely that syndrome- and modality-specific profiles are relative rather than absolute, and phenomenologically similar deficits could have distinct cognitive mechanisms. This is an important issue for future study.

Visual inspection of the individual profiles of atrophy in PNFA and semantic dementia patients (Fig. 2) suggests possible anatomical bases for the group-level differences and within-group variation in auditory performance. The profiles observed—variable peri-Sylvian atrophy in PNFA and more focal and more uniform, leftward-asymmetric anterior temporal lobe atrophy in semantic dementia—are consistent with previous anatomical evidence in these PPA syndromes (Mesulam, 1982, 2003; Nestor *et al*., 2003; Gorno-Tempini *et al*., 2004; Hodges and Patterson, 2007; Rohrer *et al*., 2008*a*, *b*, 2009). The more marked involvement of posterior peri-Sylvian cortices in the PNFA group would predict deficits at earlier auditory cortical processing stages based on the evidence from normal subjects (Griffiths and Warren, 2002; Lewis *et al*., 2005; Warren *et al*., 2005*b*; Zaehle *et al*., 2008), while individual variation in the extent of posterior damage would allow for variation in the prominence of such deficits across the PNFA group (Fig. 3). It is also clear that patients with PNFA have involvement of higher order anterior peri-Sylvian and inferior parietal areas that might potentially contribute to conjoint deficits of semantic processing of complex sounds (Engelien *et al*., 1995, 2006; Lewis *et al*., 2004, 2005, 2009; Thierry and Price, 2006). In contrast, the more stereotypical involvement of the anterior left temporal lobe and anterior peri-Sylvian cortex in semantic dementia patients would provide a substrate for the more restricted, multimodal deficit of semantic processing exhibited by these patients (Bozeat *et al*., 2000; Lambon Ralph *et al*., 2001; Coccia *et al*., 2004; Hodges and Patterson, 2007; Rami *et al*., 2007). Quantitative cross-sectional and longitudinal analyses in larger PPA cohorts will be required to substantiate these functional anatomical relationships.

This study has addressed deficits of auditory processing identified in a consecutive series of patients with PPA: i.e. we have used a 'lesion-led' approach. However, an uncertain proportion of patients with PPA syndromes present with prominent symptoms of central auditory dysfunction: a number of cases have been described with progressive word deafness or agnosia for non-verbal sounds as leading features, many in the Japanese literature (Confavreux *et al*., 1992; Otsuki *et al*., 1998; Kuramoto *et al*., 2002; Kaga *et al*., 2004; Yamamoto *et al*., 2004; Uttner *et al*., 2006; Iizuka *et al*., 2007; Jörgens *et al*., 2008). The auditory deficits in these cases have not been systematically characterized; however, the available evidence suggests that most have a clinical syndrome aligned with PNFA, comprising speech production failure with variably salient accompanying features, including dysprosody, dysarthria, working memory impairment, parietal signs and behavioural disturbance. Anatomically, such cases have bilateral, often asymmetric peri-Sylvian atrophy or hypometabolism. The defect of early perceptual analysis of non-verbal sounds identified in the PNFA group here suggests a possible basis for clinical syndromes of word deafness and auditory agnosia that develop in some patients. In this regard, we note the wide variation in performance of our PNFA patients on the early perceptual and apperceptive auditory tests (Fig. 3), raising the possibility of discrete subgroups with more severe auditory impairment within the PNFA spectrum. This would be consistent with the considerable anatomical and pathological heterogeneity of PNFA, which is

in contrast to the relatively uniform profile of semantic dementia (Rohrer *et al*., 2008*a*).

The relationship between auditory dysfunction and impaired speech output is of considerable interest in those patients with clinically evident auditory agnosias and in the PNFA group more broadly. There are a number of potential mechanisms by which deficits of complex sound analysis could impair speech production. Anatomically, analysis of incoming auditory signals, speech output and monitoring of own voice are linked via the dorsal auditory cortical pathway(s) between frontal, parietal and posterior superior temporal cortices (Warren *et al*., 2005*b*). Functionally, sensori–motor interactions mediated by this dorsal pathway have been shown to modulate spoken output in healthy individuals (Wilson *et al*., 2006) and in patients with focal brain damage (Racette *et al*., 2006), perhaps by transforming, or failing to transform faithfully, stored templates for auditory objects (in particular, phonemes) into motor programmes. By a mechanism of this kind, degraded processing of complex sounds from cortical degeneration in the region of the posterior temporal lobe/temporo-parietal junction might, via linked cortical processing stages, affect mechanisms of speech output mediated by more anterior cortical regions. This possibility does not of course exclude concurrent primary involvement of the speech output mechanisms proper (indeed, that would be anticipated with a neurodegenerative process).

Taken together, the present findings argue for the existence of core disorders of complex non-verbal sound perception and recognition in PPA and for specific disorders at perceptual and semantic levels of analysis in PNFA and semantic dementia, respectively. Our findings have clear clinical and pathophysiological implications. Clinically, the findings define the PPA syndromes more fully and provide a framework for understanding the symptoms of altered auditory function reported by a proportion of patients with PPA (Confavreux *et al*., 1992; Bozeat *et al*., 2000; Uttner *et al*., 2006; Griffiths *et al*., in press) Disorders of non-verbal sound processing in the PPA spectrum may be more widespread and significant than previously recognized: auditory complaints in these 'language-based dementias' should not be uncritically ascribed to peripheral hearing loss. Pathophysiologically, the existence of non-verbal auditory agnosias in these PPA subtypes argues for the existence of fundamental disorders of cortical information processing, affecting other kinds of complex auditory information besides speech. In the case of semantic dementia, this interpretation is constant with a multimodal deficit of knowledge stores anticipated by substantial neuropsychological evidence; in the case of PNFA, it raises the possibility that a generic derangement of complex sound analysis might underpin at least a proportion of cases of progressive disintegration of speech processing. To establish a precise brain basis for the auditory signatures identified here is likely to be challenging, particularly for PNFA: previous evidence from the study of focal lesions in aphasic stroke suggests a close correlation between verbal and non-verbal dysfunction but only a loose correlation between particular non-verbal deficits and anatomical substrates (Adriani *et al*., 2003; Saygin *et al*., 2003), and this issue is likely to be amplified in degenerative pathologies. We propose non-verbal analogues of cortical language network dysfunction in PPA syndromes (Sonty *et al*., 2007): verbal and non-verbal dysfunction might jointly result from the degraded exchange of information between distributed cortical areas in the temporal and frontal lobes. Clear directions for future work include more detailed analysis of component processes that underpin complex sound defects in different PPA syndromes; the application of anatomical, functional and connectivity based brain imaging modalities that can delineate areas of pathophysiological as well as structural damage; systematic clinico-pathological correlation across the PPA spectrum; and tracking of the evolution of non-verbal deficits in relation to the language deficits that characterize the PPA syndromes.

Acknowledgements

We are grateful to the subjects for their participation. We thank Prof. Elizabeth Warrington, Dr Josephine Barnes, and Dr Gerard Ridgway for helpful discussion. This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer's Research Trust Co-ordinating Centre.

Funding

Medical Research Council UK; Medical Research Council Capacity Building PhD Studentship (to J.C.G.); Alzheimer's Research Trust Fellowship (to S.J.C.); Wellcome Trust Research Training Fellowship (to J.D.R.); Wellcome Trust Intermediate Clinical Fellowship (to J.D.W.).

Supplementary material

Supplementary material is available at *Brain* online.

References

Adriani M, Maeder P, Meuli R, Thiran AB, Frischknecht R, Villemure JG, et al. Sound recognition and localization in man: specialized cortical networks and effects of acute circumscribed lesions. Exp Brain Res 2003; 153: 591–604.

Anaki D, Kaufman Y, Freedman M, Moscovitch M. Associative (prosop) agnosia without (apparent) perceptual deficits: a case-study. Neuropsychologia 2007; 45: 1658–71.

Bishop DV. Test for reception of grammar. Cambridge: MRC Applied Psychology Unit; 1989.

Blesser B. Speech perception under conditions of spectral transformation. I. Phonetic characteristics. J Speech Hear Res 1972; 15: 5–41.

Bozeat S, Lambon Ralph MA, Patterson K, Garrard P, Hodges JR. Non-verbal semantic impairment in semantic dementia. Neuropsychologia 2000; 38: 1207–15.

Chi T, Ru P, Shamma SA. Multiresolution spectrotemporal analysis of complex sounds. J Acoust Soc Am 2005; 118: 887–906.

Clarke S, Bellmann A, De Ribaupierre F, Assal G. Non-verbal auditory recognition in normal subjects and brain-damaged patients: evidence for parallel processing. Neuropsychologia 1996; 34: 587–603.

Coccia M, Bartolini M, Luzzi S, Provinciali L, Lambon Ralph MA. Semantic memory is an amodal, dynamic system: evidence from the interaction of naming and object use in semantic dementia. Cognitive Neuropsychology 2004; 21: 513–27.

Confavreux C, Croisile B, Garassus P, Aimard G, Trillet M. Progressive amusia and aprosody. Arch Neurol 1992; 49: 971–6.

Crutch SJ, Warrington EK. The Influence of refractoriness upon comprehension of non-verbal auditory stimuli. Neurocase 2008; 14: 494–507.

Davis A. Hearing in adults: the prevalence and distribution of hearing impairment and reported hearing disability in the MRC Institute of Hearing Research's National Study of Hearing. London: Whurr Publishers; 1995.

De Renzi E, Scotti G, Spinnler H. Perceptual and associative disorders of visual recognition. Relationship to the side of the cerebral lesion. Neurology 1969; 19: 634–42.

Delis DC, Kaplan E, Kramer JH. D-KEFS). S.l. Delis-Kaplan executive function system. San Antonio: The Psychological Corporation; 2001.

Dunn LM, Dunn LM, Whetton C, Pintilie D. British Picture Vocabulary Scale. Windsor: NFER-Nelson; 1982.

Engelien A, Silbersweig D, Stern E, Huber W, Doring W, Frith C, et al. The functional anatomy of recovery from auditory agnosia. A PET study of sound categorization in a neurological patient and normal controls. Brain 1995; 118 (Pt 6): 1395–409.

Engelien A, Tuscher O, Hermans W, Isenberg N, Eidelberg D, Frith C, et al. Functional neuroanatomy of non-verbal semantic sound processing in humans. J Neural Transm 2006; 113: 599–608.

Folstein MF, Folstein SE, McHugh PR. ''Mini-mental state'': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Gainotti G, Barbier A, Marra C. Slowly progressive defect in recognition of familiar people in a patient with right anterior temporal atrophy. Brain 2003; 126: 792–803.

Garrard P, Carroll E. Lost in semantic space: a multi-modal, non-verbal assessment of feature knowledge in semantic dementia. Brain 2006; 129: 1152–63.

Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, et al. Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol 2004; 55: 335–46.

Griffiths TD, Bamiou D-E, Warren JD. Disorders of the auditory brain. In: Palmer AR, Rees A, editors. Oxford Handbook of Auditory Science: The Auditory Brain. Oxford: Oxford University Press (in press).

Griffiths TD, Rees A, Green G. Disorders of human complex sound processing. Neurocase 1999; 5: 365–78.

Griffiths TD, Warren JD. The planum temporale as a computational hub. Trends Neurosci 2002; 25: 348–53.

Griffiths TD, Warren JD. What is an auditory object? Nat Rev Neurosci 2004; 5: 887–92.

Hodges JR, Patterson K. Semantic dementia: a unique clinicopathological syndrome. Lancet Neurol 2007; 6: 1004–14.

Hovius M, Kellenbach ML, Graham KS, Hodges JR, Patterson K. What does the object decision task measure? Reflections on the basis of evidence from semantic dementia. Neuropsychology 2003; 17: 100–7.

Iizuka O, Suzuki K, Endo K, Fujii T, Mori E. Pure word deafness and pure anarthria in a patient with frontotemporal dementia. Eur J Neurol 2007; 14: 473–5.

Jörgens S, Biermann-Ruben K, Kurz MW, Flügel C, Daehli Kurz K, Antke C, et al. Word deafness as a cortical auditory processing deficit: a case report with MEG. Neurocase 2008; 14: 307–16.

Joubert S, Felician O, Barbeau E, Sontheimer A, Barton JJ, Ceccaldi M, et al. Impaired configurational processing in a case of progressive prosopagnosia associated with predominant right temporal lobe atrophy. Brain 2003; 126: 2537–50.

Kaga K, Nakamura M, Takayama Y, Momose H. A case of cortical deafness and anarthria. Acta Otolaryngol 2004; 124: 202–5.

Kuramoto S, Hirano T, Uyama E, Tokisato K, Miura M, Watanabe S, et al. A case of slowly progressive aphasia accompanied with auditory agnosia. Rinsho Shinkeigaku 2002; 42: 299–303.

Kveraga K, Ghuman AS, Bar M. Top-down predictions in the cognitive brain. Brain Cogn 2007; 65: 145–68.

Lambon Ralph MA, McClelland JL, Patterson K, Galton CJ, Hodges JR. No right to speak? The relationship between object naming and semantic impairment: neuropsychological evidence and a computational model. J Cogn Neurosci 2001; 13: 341–56.

Lewis JW, Brefczynski JA, Phinney RE, Janik JJ, DeYoe EA. Distinct cortical pathways for processing tool versus animal sounds. J Neurosci 2005; 25: 5148–58.

Lewis JW, Talkington WJ, Walker NA, Spirou GA, Jajosky A, Frum C, et al. Human cortical organization for processing vocalizations indicates representation of harmonic structure as a signal attribute. J Neurosci 2009; 29: 2283–96.

Lewis JW, Wightman FL, Brefczynski JA, Phinney RE, Binder JR, DeYoe EA. Human brain regions involved in recognizing environmental sounds. Cereb Cortex 2004; 14: 1008–21.

McCarthy R, Warrington EK. A two-route model of speech production. Evidence from aphasia. Brain 1984; 107 (Pt 2): 463–85.

Mesulam MM. Slowly progressive aphasia without generalized dementia. Ann Neurol 1982; 11: 592–8.

Mesulam MM. Primary progressive aphasia—a language-based dementia. N Engl J Med 2003; 349: 1535–42.

Mohs RC, Knopman D, Petersen RC, Ferris SH, Ernesto C, Grundman M, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11 (Suppl 2): S13–21.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546–54.

Nestor PJ, Graham NL, Fryer TD, Williams GB, Patterson K, Hodges JR. Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. Brain 2003; 126: 2406–18.

Otsuki M, Soma Y, Sato M, Homma A, Tsuji S. Slowly progressive pure word deafness. Eur Neurol 1998; 39: 135–40.

Peretz I, Kolinsky R, Tramo M, Labrecque R, Hublet C, Demeurisse G, et al. Functional dissociations following bilateral lesions of auditory cortex. Brain 1994; 117: 1283–301.

Racette A, Bard C, Peretz I. Making non-fluent aphasics speak: sing along!. Brain 2006; 129: 2571–84.

Raven J, Raven JC, Court JH. Section 1. Manual for Raven's Progressive Matrices and Vocabulary Scales. San Antonio, TX: General Overview.Harcourt Assessment; 2003.

Rami L, Loy CT, Hailstone J, Warren JD. Odour identification in frontotemporal lobar degeneration. J Neurol 2007; 254: 431–5.

Reitan RM. A manual for the administrating and scoring of the Trail Making Test. Indianapolis, IN, USA: Indiana University Press; 1959.

Rogers TT, Lambon Ralph MA, Garrard P, Bozeat S, McClelland JL, Hodges JR, et al. Structure and deterioration of semantic memory: a neuropsychological and computational investigation. Psychol Rev 2004; 111: 205–35.

Rohrer JD, Knight WD, Warren JE, Fox NC, Rossor MN, Warren JD. Word-finding difficulty: a clinical analysis of the progressive aphasias. Brain 2008a; 131: 8–38.

Rohrer JD, McNaught E, Foster J, Clegg SL, Barnes J, Omar R, et al. Tracking progression in frontotemporal lobar degeneration: serial MRI in semantic dementia. Neurology 2008b; 71: 1445–51.

Rohrer JD, Warren JD, Modat M, Ridgway GR, Douiri A, Rossor MN, et al. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. Neurology 2009; 72: 1562–9.

Saygin AP, Dick F, Wilson SM, Dronkers NF, Bates E. Neural resources for processing language and environmental sounds: evidence from aphasia. Brain 2003; 126: 928–45.

Scott SK, Blank CC, Rosen S, Wise RJ. Identification of a pathway for intelligible speech in the left temporal lobe. Brain 2000; 123 (Pt 12): 2400–6.

Sonty SP, Mesulam MM, Weintraub S, Johnson NA, Parrish TB, Gitelman DR. Altered effective connectivity within the language

network in primary progressive aphasia. J Neurosci 2007; 27: 1334–45.
Taylor A, Warrington EK. Visual agnosia: a single case report. Cortex 1971; 7: 152–61.
Thierry G, Price CJ. Dissociating verbal and nonverbal conceptual processing in the human brain. J Cogn Neurosci 2006; 18: 1018–28.
Uttner I, Mottaghy FM, Schreiber H, Riecker A, Ludolph AC, Kassubek J. Primary progressive aphasia accompanied by environmental sound agnosia: a neuropsychological, MRI and PET study. Psychiatry Res 2006; 146: 191–7.
Warren JD, Jennings AR, Griffiths TD. Analysis of the spectral envelope of sounds by the human brain. Neuroimage 2005a; 24: 1052–7.
Warren JE, Wise RJ, Warren JD. Sounds do-able: auditory-motor transformations and the posterior temporal plane. Trends Neurosci 2005b; 28: 636–43.
Warrington EK. The selective impairment of semantic memory. Q J Exp Psychol 1975; 27: 635–57.
Warrington EK. The Camden memory tests. East Sussex, UK: manual. Psychology Press; 1996.
Warrington EK, James M. An experimental investigation of facial recognition in patients with unilateral cerebral lesions. Cortex 1967; 3: 317–26.
Warrington EK, James M. The visual object and space perception battery. Bury St. Edmunds: Thames Valley Test Company; 1991.
Warrington EK, McKenna P, Orpwood L. Single Word Comprehension: A Concrete and Abstract Word Synonym Test. Neuropsychol Rehabil 1998; 8: 143–54.
Wilson SM, Iacoboni M. Neural responses to non-native phonemes varying in producibility: evidence for the sensorimotor nature of speech perception. Neuroimage 2006; 33: 316–25.
Yamamoto T, Kikuchi T, Nagae J, Ogata K, Ogawa M, Kawai M. Dysprosody associated with environmental auditory sound agnosia in right temporal lobe hypoperfusion—a case report. Rinsho Shinkeigaku 2004; 44: 28–33.
Zaehle T, Geiser E, Alter K, Jancke L, Meyer M. Segmental processing in the human auditory dorsal stream. Brain Res 2008; 1220: 179–90.